

# ***AHRQ Healthcare Horizon Scanning System – Potential High-Impact Interventions Report***

---

## **Priority Area 03: Cardiovascular Disease**

**Prepared for:**

Agency for Healthcare Research and Quality  
U.S. Department of Health and Human Services  
540 Gaither Road  
Rockville, MD 20850  
[www.ahrq.gov](http://www.ahrq.gov)

**Contract No. HHSA290201000006C**

**Prepared by:**

ECRI Institute  
5200 Butler Pike  
Plymouth Meeting, PA 19462

**December 2012**

## **Statement of Funding and Purpose**

This report incorporates data collected during implementation of the Agency for Healthcare Research and Quality (AHRQ) Healthcare Horizon Scanning System by ECRI Institute under contract to AHRQ, Rockville, MD (Contract No. HHSA290201000006C). The findings and conclusions in this document are those of the authors, who are responsible for its content, and do not necessarily represent the views of AHRQ. No statement in this report should be construed as an official position of AHRQ or of the U.S. Department of Health and Human Services.

This report's content should not be construed as either endorsements or rejections of specific interventions. As topics are entered into the System, individual topic profiles are developed for technologies and programs that appear to be close to diffusion into practice in the United States. Those reports are sent to various experts with clinical, health systems, health administration, and/or research backgrounds for comment and opinions about potential for impact. The comments and opinions received are then considered and synthesized by ECRI Institute to identify interventions that experts deemed, through the comment process, to have potential for high impact. Please see the methods section for more details about this process. This report is produced twice annually and topics included may change depending on expert comments received on interventions issued for comment during the preceding 6 months.

A representative from AHRQ served as a Contracting Officer's Technical Representative and provided input during the implementation of the horizon scanning system. AHRQ did not directly participate in horizon scanning, assessing the leads for topics, or providing opinions regarding potential impact of interventions.

## **Disclaimer Regarding 508-Compliance**

Individuals using assistive technology may not be able to fully access information in this report. For assistance contact [info@ahrq.gov](mailto:info@ahrq.gov).

## **Financial Disclosure Statement**

None of the individuals compiling this information has any affiliations or financial involvement that conflicts with the material presented in this report.

## **Public Domain Notice**

This document is in the public domain and may be used and reprinted without special permission. Citation of the source is appreciated.

**Suggested citation:** ECRI Institute. AHRQ Healthcare Horizon Scanning System Potential High-Impact Interventions: Priority Area 03: Cardiovascular. (Prepared by ECRI Institute under Contract No. HHSA290201000006C.) Rockville, MD: Agency for Healthcare Research and Quality. December 2012. <http://www.effectivehealthcare.ahrq.gov/reports/final.cfm>.

## Preface

The purpose of the AHRQ Healthcare Horizon Scanning System is to conduct horizon scanning of emerging health care technologies and innovations to better inform patient-centered outcomes research investments at AHRQ through the Effective Health Care Program. The Healthcare Horizon Scanning System provides AHRQ a systematic process to identify and monitor emerging technologies and innovations in health care and to create an inventory of interventions that have the highest potential for impact on clinical care, the health care system, patient outcomes, and costs. It will also be a tool for the public to identify and find information on new health care technologies and interventions. Any investigator or funder of research will be able to use the AHRQ Healthcare Horizon Scanning System to select potential topics for research.

The health care technologies and innovations of interest for horizon scanning are those that have yet to diffuse into or become part of established health care practice. These health care interventions are still in the early stages of development or adoption, except in the case of new applications of already-diffused technologies. Consistent with the definitions of health care interventions provided by the Institute of Medicine and the Federal Coordinating Council for Comparative Effectiveness Research, AHRQ is interested in innovations in drugs and biologics, medical devices, screening and diagnostic tests, procedures, services and programs, and care delivery.

Horizon scanning involves two processes. The first is identifying and monitoring new and evolving health care interventions that are purported to or may hold potential to diagnose, treat, or otherwise manage a particular condition or to improve care delivery for a variety of conditions. The second is analyzing the relevant health care context in which these new and evolving interventions exist to understand their potential impact on clinical care, the health care system, patient outcomes, and costs. It is NOT the goal of the AHRQ Healthcare Horizon Scanning System to make predictions on the future use and costs of any health care technology. Rather, the reports will help to inform and guide the planning and prioritization of research resources.

We welcome comments on this Potential High Impact report. Send comments by mail to the Task Order Officer named in this report to: Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, or by email to: [effectivehealthcare@ahrq.hhs.gov](mailto:effectivehealthcare@ahrq.hhs.gov).

Carolyn M. Clancy, M.D.  
Director  
Agency for Healthcare Research and Quality

Jean Slutsky, P.A., M.S.P.H.  
Director, Center for Outcomes and Evidence  
Agency for Healthcare Research and Quality

Elise Berliner, Ph.D.  
Task Order Officer  
Center for Outcomes and Evidence  
Agency for Healthcare Research and Quality

# Contents

Executive Summary .....	ES-1
Background.....	ES-1
Methods .....	ES-1
Results.....	ES-2
Discussion.....	ES-3
Arrhythmia Interventions .....	1
Cardiac Pacing System (Revo) for Patients Who May Require Future Magnetic Resonance Imaging.....	2
Subcutaneous Implantable Cardioverter-Defibrillator (S-ICD) for Treatment of Life-Threatening Ventricular Tachyarrhythmias.....	5
Brain Aneurysm Intervention.....	8
Endovascular Pipeline Embolization Device (PED) for Treatment of Giant and Wide-Necked Intracranial Aneurysms .....	9
Heart Failure Interventions.....	13
Autologous Mesenchymal Stem Cell Therapy (C-Cure) for Heart Failure.....	14
Portable Freedom Driver for In-Home Support of the Total Artificial Heart .....	17
Hypertension Intervention.....	19
Catheter-Based Radiofrequency Ablation (Symplicity System) Renal Denervation for Treatment-Resistant Hypertension .....	20
Valve and Structural Disorder Interventions.....	23
Percutaneous Annuloplasty (Carillon Mitral Contour System) for Treatment of Functional Mitral Regurgitation .....	24
Transcatheter Aortic Valve Implantation (CoreValve; Sapien) for Treatment of Severe Aortic Stenosis.....	27
Transcatheter Mitral Valve Repair (MitraClip) for Treatment of Mitral Regurgitation .....	31
References .....	35

## Figures

Figure 1. Overall high-impact potential: cardiac pacing system (Revo) for patients who may require future magnetic resonance imaging.....	3
Figure 2. Overall high-impact potential: Subcutaneous Implantable Cardioverter-Defibrillator (S-ICD) for treatment of life-threatening ventricular tachyarrhythmias.....	6
Figure 3. Overall high-impact potential: endovascular Pipeline Embolization Device (PED) for treatment of giant and wide-necked intracranial aneurysms.....	11

Figure 4. Overall high-impact potential: autologous mesenchymal stem cell therapy (C-Cure) for heart failure .....	15
Figure 5. Overall high-impact potential: Portable Freedom Driver for in-home support of the Total Artificial Heart.....	18
Figure 6. Overall high-impact potential: catheter-based radiofrequency ablation (Symplicity System) renal denervation for treatment-resistant hypertension .....	21
Figure 7. Overall high-impact potential: percutaneous annuloplasty (Carillon Mitral Contour System) for treatment of functional mitral regurgitation.....	25
Figure 8. Overall high-impact potential: transcatheter aortic valve implantation (CoreValve; Sapien) for treatment of severe aortic stenosis .....	29
Figure 9. Overall high-impact potential: transcatheter mitral valve repair (MitraClip) for treatment of mitral regurgitation.....	32

# Executive Summary

## Background

Horizon scanning is an activity undertaken to identify technological and system innovations that could have important impacts or bring about paradigm shifts. In the health care sector, horizon scanning pertains to identifying new (and new uses of existing) pharmaceuticals, medical devices, diagnostic tests and procedures, therapeutic interventions, rehabilitative interventions, behavioral health interventions, and public health and health promotion activities. In early 2010, the Agency for Healthcare Research and Quality (AHRQ) identified the need to establish a national Healthcare Horizon Scanning System to generate information to inform comparative-effectiveness research investments by AHRQ and other interested entities. AHRQ makes those investments in 14 priority areas. For purposes of horizon scanning, AHRQ's interests are broad and encompass drugs, devices, procedures, treatments, screening and diagnostics, therapeutics, surgery, programs, and care delivery innovations that address unmet needs. Thus, we refer to topics identified and tracked in the AHRQ Healthcare Horizon Scanning System generically as "interventions." The AHRQ Healthcare Horizon Scanning System implementation of a systematic horizon scanning protocol (developed between September 1 and November 30, 2010) began on December 1, 2010. The system is intended to identify interventions that purport to address an unmet need and are up to 7 years out on the horizon and then to follow them for up to 2 years after initial entry into the health care system. Since that implementation, review of more than 15,000 leads about potential topics has resulted in identification and tracking of about 1,600 topics across the 14 AHRQ priority areas and 1 cross-cutting area; about 950 topics are being actively tracked in the system.

## Methods

As part of the Healthcare Horizon Scanning System activity, a report on interventions deemed as having potential for high impact on some aspect of health care or the health care system (e.g., patient outcomes, utilization, infrastructure, costs) is aggregated twice annually. Topics eligible for inclusion are those interventions expected to be within 0–4 years of potential diffusion (e.g., in phase III trials or for which some preliminary efficacy data in the target population are available) in the United States or that have just begun diffusing and that have completed an expert feedback loop.

The determination of impact is made using a systematic process that involves compiling information on topics and issuing topic drafts to a small group of various experts (selected topic by topic) to gather their opinions and impressions about potential impact. Those impressions are used to determine potential impact. Information is compiled for expert comment on topics at a granular level (i.e., similar drugs in the same class are read separately), and then topics in the same class of a device, drug, or biologic are aggregated for discussion and impact assessment at a class level for this report. The process uses a topic-specific structured form with text boxes for comments and a scoring system (1 minimal to 4 high) for potential impact in seven parameters. Participants are required to respond to all parameters.

The scores and opinions are then synthesized to discern those topics deemed by experts to have potential for high impact in one or more of the parameters. Experts are drawn from an expanding database ECRI Institute maintains of approximately 350 experts nationwide who were invited and agreed to participate. The experts comprise a range of generalists and specialists in the health care sector whose experience reflects clinical practice, clinical research, health care delivery, health business, health technology assessment, or health facility administration perspectives. Each expert uses the structured form to also disclose any potential intellectual or financial conflicts of interest

(COIs). Perspectives of an expert with a COI are balanced by perspectives of experts without COIs. No more than two experts with a possible COI are considered out of a total of the seven or eight experts who are sought to provide comment for each topic. Experts are identified in the system by the perspective they bring (e.g., clinical, research, health systems, health business, health administration, health policy).

The topics included in this report had scores *and/or* supporting rationales at or above the overall average for all topics in this priority area that received comments by experts. Of key importance is that topic scores alone are not the sole criterion for inclusion—experts’ rationales are the main drivers for the designation of potentially high impact. We then associated topics that emerged as having potentially high impact with a further subcategorization of “lower,” “moderate,” or “higher” within the potential high-impact range. As the Healthcare Horizon Scanning System grows in number of topics on which expert opinions are received, and as the development status of the interventions changes, the list of topics designated as having potentially high impact is expected to change over time. This report is being generated twice a year.

For additional details on methods, please refer to the full AHRQ Healthcare Horizon Scanning System Protocol and Operations Manual published on AHRQ’s Effective Health Care Web site.

## Results

The table below lists the 25 topics for which (1) preliminary phase III data for drugs, at least phase II data for devices and procedures, or some human data for off-label uses or programs were available; (2) information was compiled before September 21, 2012, in this priority area; *and* (3) we received six to nine sets of comments from experts between December 15, 2011, and October 10, 2012. (Ninety-nine topics in this priority area were being tracked in the system as of October 26, 2012.) For purposes of the Potential High-Impact Interventions Report, we aggregated related topics for summary and discussion (e.g., individual drugs into a class). We present 9 summaries on 10 topics (indicated below by an asterisk) that emerged as having potential for high impact on the basis of experts’ comments. The material on interventions in this Executive Summary and report is organized alphabetically by disease state and interventions within that disease state. Readers are encouraged to read the detailed information on each intervention that follows the Executive Summary.

### Priority Area 03: Cardiovascular

Topic	High-Impact Potential
1. Altitude training using a portable simulation chamber for treatment of heart failure	No high-impact potential at this time
2. Apo-B synthesis inhibitor (mipomersen) for treatment of familial hypercholesterolemia	No high-impact potential at this time
3. * Autologous mesenchymal stem cell therapy (C-Cure) for heart failure	High
4. Baroreflex stimulation for treatment of drug-resistant hypertension	No high-impact potential at this time
5. * Cardiac pacing system (Revo) for patients who may require future magnetic resonance imaging	Lower end of the potential high-impact range
6. * Catheter-based radiofrequency ablation (Symplicity System) renal denervation for treatment-resistant hypertension	Lower end of the potential high-impact range
7. * Endovascular Pipeline Embolization Device (PED) for treatment of giant and wide-necked intracranial aneurysms	Lower end of the potential high-impact range
8. Factor Xa inhibitor (apixaban) for anticoagulation	No high-impact potential at this time
9. Factor Xa inhibitor (edoxaban) for anticoagulation	No high-impact potential at this time
10. Factor Xa inhibitor (rivaroxaban) for anticoagulation	No high-impact potential at this time

Topic	High-Impact Potential
11. Low-dose tPA for treatment of intraventricular hemorrhage	No high-impact potential at this time
12. Magnetically levitated centrifugal pump ventricular-assist device (DuraHeart) as bridge to transplantation for end-stage heart failure	No high-impact potential at this time
13. Magnetically levitated centrifugal pump ventricular-assist device (HeartWare) as bridge to transplantation for end-stage heart failure	No high-impact potential at this time
14. Magnetically levitated centrifugal pump ventricular-assist device (HeartWare) as destination therapy for end-stage heart failure	No high-impact potential at this time
15. MTP inhibitor (lomitapide) for treatment of homozygous familial hypercholesterolemia	No high-impact potential at this time
16. Off-label minocycline with tPA for treatment of stroke	No high-impact potential at this time
17. Off-label sildenafil (Revatio, Viagra) for improvement in pediatric exercise tolerance post-Fontan operation	No high-impact potential at this time
18. * Percutaneous annuloplasty (Carillon Mitral Contour System) for treatment of functional mitral regurgitation	Moderately high
19. * Portable Freedom Driver for in-home support of the Total Artificial Heart	Lower end of the potential high-impact range
20. Robotic system (CorPath 200) for remotely controlled percutaneous coronary intervention	No high-impact potential at this time
21. Standardized protocol and integrated system (RACE Project) for treatment and transfer of patients with ST-elevation myocardial infarction	No high-impact potential at this time
22. * Subcutaneous Implantable Cardioverter-Defibrillator (S-ICD) for treatment of life-threatening ventricular tachyarrhythmias	Lower end of the potential high-impact range
23. * Transcatheter aortic valve implantation (CoreValve) for treatment of severe aortic stenosis	High
24. * Transcatheter aortic valve implantation (Sapien) for treatment of severe aortic stenosis	High
25. * Transcatheter mitral valve repair (MitraClip) for treatment of mitral regurgitation	High

## Discussion

Research activity in all disease areas of the cardiovascular priority area is robust and addresses both novel and incremental innovations that could affect patient outcomes, shift care models, and affect costs and care delivery.

## Arrhythmia

According to the American Heart Association (AHA), arrhythmias (abnormal heartbeats) are a major source of cardiovascular-related morbidity and mortality. Ventricular tachycardia (rapid heartbeat) and ventricular fibrillation (unsynchronized heartbeat) reduce the heart's pumping ability and can cause collapse, cardiac arrest, and sudden death. These conditions are believed to contribute to the more than 400,000 deaths from sudden cardiac arrest that occur in the United States each year. Numerous drugs and implantable devices exist to treat arrhythmia. Unfortunately, drugs for rhythm and rate control carry significant risks of adverse events, and available implantable devices often contraindicate certain procedures (e.g., magnetic resonance imaging [MRI]). Therefore, a significant unmet need exists for better and safer treatments for patients with various forms of cardiac arrhythmia. Experts highlighted two devices that could be of potentially high impact in treating arrhythmia.



## Cardiac Pacing System (Revo) for Patients Who May Require Future Magnetic Resonance Imaging

- **Key Facts:** To address concerns about pacemaker-compatible MRI imaging, a new pacemaker was developed and, in February 2011, approved for marketing. The Revo MRI™ Sure Scan® pacing system (Medtronic, Inc., Minneapolis, MN) is a dual-lead, electronic, implantable, cardiac pacemaker engineered to allow patients to safely undergo MRI scans under specific conditions. The U.S. Food and Drug Administration (FDA) approved the device as “MR-conditional,” meaning that it can be used in an MRI environment under certain conditions according to the type of MRI scanner and scanner settings. A phase III trial of 464 patients reported that no MRI-related complications—which include sustained ventricular arrhythmias, pacemaker inhibition or output failures, electrical resets, or other pacemaker malfunctions—occurred during or after MRI procedures. The list price for the Revo is \$13,000, according to Medtronic. Hospitals and group purchasing organizations typically negotiate significant discounts on such devices. The U.S. Centers for Medicare & Medicaid Services (CMS) issued a final coverage memorandum in July 2011 related to the Revo, stating that “the evidence is adequate to conclude that magnetic resonance imaging (MRI) improves health outcomes for Medicare beneficiaries with implanted permanent pacemakers (PMs) when the PMs are used according to the FDA-approved labeling for use in an MRI environment.”
- **Key Expert Comments:** Experts commenting on this new device were divided about its potential impact. Experts agreed that having the capability to conduct MRI scans in patients with pacemakers is important. However, experts also noted that novel protocols are being investigated to determine whether conventional pacemakers can also be used in this capacity, which could obviate the need for the Revo. Although experts thought acceptance of the device would be high by both clinicians and patients, the device’s cost, training requirements, and lack of pacing-efficacy and safety data might temper its diffusion.
- **Potential for High Impact:** Lower end of the potential high-impact range

## Subcutaneous Implantable Cardioverter-Defibrillator (S-ICD) for Treatment of Life-Threatening Ventricular Tachyarrhythmias

- **Key Facts:** The standard available implantable cardioverter-defibrillators (ICDs) that are intended to prevent sudden cardiac death by treating ventricular tachyarrhythmias require implanting a transvenous lead in the heart. Complications that arise from ICD implantation are often related to the lead-implantation portion of the procedure. Additionally, lead failure is a major limitation with ICD implantation, and procedures to remove these faulty leads are often associated with morbidity and mortality. The Subcutaneous Implantable Cardioverter-Defibrillator (S-ICD®) System (Boston Scientific Corp., Natick, MA) is a subcutaneous ICD that is intended to be minimally invasive and does not require electrode leads to be placed in or on the heart. Furthermore, the device does not require imaging equipment for placement because the system components are designed to be positioned using only anatomic landmarks. The S-ICD was FDA approved in September 2012, and the company expected a launch by late fall 2012. Some third-party payers have developed policies that mention the S-ICD; other have not updated their policies since the September FDA approval and exclude the device from coverage citing lack of FDA approval. CMS has a national coverage determination for ICDs and criteria for coverage but does not specifically mention the S-ICD system. The cost of the device is reported to be similar to that of conventional ICDs; however, the procedure is purported to take less time to perform because it can be performed

in an outpatient setting with no need for fluoroscopy, imaging, or an electrophysiology laboratory.

- **Key Expert Comments:** Experts were somewhat optimistic that this intervention has some potential to improve patient health outcomes by reducing complications associated with lead-based ICDs and associated secondary surgeries that carry a high risk of morbidity and some mortality. This optimism was diluted partially by a couple of experts who suggested that this device's limited pacing capabilities would temper widespread diffusion and impact. Because the implantation procedure requires fewer resources and can be performed in an outpatient setting, this intervention could shift care delivery to a less invasive setting and result in shorter hospital stays than for conventional ICD implantation and possibly lower costs associated with the procedure.
- **Potential for High Impact:** Lower end of the potential high-impact range

## Brain Aneurysm

A brain aneurysm, or intracranial aneurysm (ICA), is a balloon-like enlargement of a brain vessel wall that occurs from a weakening of the vessel wall and puts the vessel at risk of rupture. According to the Brain Aneurysm Foundation, an estimated 1 in 50 people in the United States have an unruptured brain aneurysm, and the annual rupture rate is 8–10 ruptures per 100,000 people. Aneurysm rupture can cause subarachnoid hemorrhage, brain damage, stroke, and death. About 40% of aneurysm ruptures are fatal, and 66% of patients who survive the rupture live with permanent neurologic deficit. Despite advancements in treating unruptured ICAs, clinical results for certain subtypes of treated ICAs remain unsatisfactory. In particular, large or giant wide-necked aneurysms are difficult to treat with standard aneurysm coils, and procedural complications are often associated with the treatment. Completely closing off a wide-necked or giant aneurysm is not always accomplished when standard coiling is used, and the recurrence rate is high; large or wide-necked aneurysms have recurrence rates of approximately 50%. Because of the challenges and risks involved with treating these aneurysm subtypes, manufacturers have developed new devices for treating these ICAs. Experts commenting on brain aneurysm topics identified one procedure they thought had potential for high impact.

## Endovascular Pipeline Embolization Device (PED) for Treatment of Giant and Wide-Necked Intracranial Aneurysms

- **Key Facts:** Patients with large or giant wide-necked ICAs face high risks for procedural complications, incomplete treatment, and aneurysm recurrence. The Pipeline<sup>®</sup> Embolization Device (PED, Covidien, plc, Dublin, Ireland) is a flow-diversion device that was FDA approved in April 2011 for endovascular treatment of large or giant wide-necked brain aneurysms of the internal carotid artery in adults. The PED is a cylindrical, stent-like device designed to be delivered to the aneurysm via a catheter. Once in place, the device is positioned across the aneurysm's neck and expanded against the vessel walls to block blood flow to the aneurysm. The company purports that the device reconstructs the parent artery to provide long-term aneurysm occlusion and restore natural blood flow. In the occluded aneurysm, blood remaining in the aneurysm clots, and the aneurysm shrinks. The PED is intended to reduce the risk of aneurysm rupture in patients with large or giant wide-necked ICAs. Researchers from Johns Hopkins University reported in the journal *Neurosurgery* in November 2012 the results of a cost-comparison performed on consecutive cases in which the PED was used (n=30; average aneurysm size 9.8 mm) and traditional stent coiling was used (n=30; average aneurysm size 7.3 mm). The researchers reported, "The total combined

costs of proximal access/guide catheters, microcatheters, and microwires were equivalent between the 2 groups. The cost of implants, however, was significantly lower in the PED group ( $\$13\,175 \pm 726$  vs  $\$19\,069 \pm 2015$ ;  $p = .013$ ), despite this group having a larger mean aneurysm size. Furthermore, the total procedure cost was significantly lower for the PED group vs the stent-coiling group ( $\$16\,445 \pm 735$  vs  $\$22\,145 \pm 2022$ ;  $p = .02$ ), a 25.7% cost reduction. This represents a 27.1% reduction in the cost per millimeter of aneurysm treated in the PED group ( $\$2261 \pm 299$ ) vs the stent-coiling group ( $\$3102 \pm 193$ ;  $p = .02$ ).” The device appears to have received wide clinical acceptance among neurovascular centers. For example, the Mayo Clinic reported that the device has replaced stent coiling in up to 20% of its aneurysm cases; use for other indications, such as smaller aneurysms and ruptured aneurysms has also been reported. Third-party payers generally cover use of the device for its labeled indications; CMS has no national coverage determination, and coverage is left to the discretion of local carriers.

- **Key Expert Comments:** Although some experts thought that the subset of patients this device intends to treat is small, all experts agreed that these patients have limited treatment options and that the PED fulfills an unmet need for these patients. Experts thought the PED has the potential to improve patient health by decreasing aneurysm recurrence and lowering the risk of aneurysm rupture and procedure-related complications. Because ICA treatment with the PED device is less invasive and is purported to result in fewer procedural complications, most experts thought this device would be widely accepted by clinicians and patients, although some experts thought the technical difficulty and learning curve of the procedure, along with the required proctoring before clinical use, might temper diffusion.
- **Potential for High Impact:** Lower end of the potential high-impact range

## Heart Failure

Heart failure (HF), a debilitating condition that adversely affects quality of life as well as life expectancy, can develop from any condition that overloads, damages, or reduces the efficiency of the heart muscle, impairing the ventricles’ ability to fill with or eject blood. According to AHA, about 5.7 million U.S. adults aged 20 years or older were living with HF in 2009. Those surviving a heart attack are the most at risk. AHA estimates that for the U.S. population 65 years of age or older, the incidence of HF is about 10 per 1,000 people. Nearly 550,000 new cases of HF occur each year. In 2005 (the most recent year for which mortality statistics are available), more than 292,000 patients died in the United States with a prior diagnosis of HF; it was listed as the underlying cause in nearly 59,000 deaths and a contributing (secondary) factor in the remaining cases. HF prevalence has increased during the past 20 years, and the number of patients who progress to end-stage HF is expected to grow because of increased survival in patients with coronary artery disease, an increased population of aging patients, and significant advances in the control of other potentially lethal diseases. Because of the clear unmet need for effective therapies for HF and its underlying cause, many new drugs, biologics, and devices are under study for treating patients with HF. Experts commenting on topics on HF identified one biologic and one device they thought have potential for high impact.

## Autologous Mesenchymal Stem Cell Therapy (C-Cure) for Heart Failure

- **Key Facts:** Available HF treatments do not reverse the disease process, and mortality from HF remains high, even when optimally treated. Optimal treatment is typically determined through trial-and-error approaches with medication regimens. A significant unmet need exists for disease-modifying therapies for HF. C-Cure<sup>®</sup>, also known as C3BS-CQR-1

(Cardio3 Biosciences, S.A., Mont-Saint-Guibert, Belgium), is a bone-marrow-derived, cardiopoietic (i.e., having cardiac cell-generating potential), mesenchymal stem cell (MSC) therapy. The developer claims it can potentially regenerate damaged heart muscle tissue without risk of rejection. The therapy involves harvesting MSCs from the patient's bone marrow, treating the cells with growth factors (a "cardiopoietic cocktail"), and then injecting the cells into the patient's heart. The cocktail includes transforming growth factor-beta1, bone morphogenetic protein-4, activin A, retinoic acid, insulin-like growth factor-1, fibroblast growth factor-2, alpha-thrombin, and interleukin-6. The company purports that treatment with these proteins can transform MSCs (which are undifferentiated) into cardiac progenitor cells to replicate natural cardiogenesis, without modifying the cell's genome. The cardiac progenitor cells are designed to behave identically to cells lost during progression of HF, and they purportedly regenerate damaged heart muscle without risk of rejection.

According to an April 2011 company press release, researchers reporting on phase II results from 45 patients with severe HF of ischemic origin who were treated with standard of care or standard of care plus C-Cure concluded, "Patients receiving C-Cure saw an 18.1% increase in left ventricular ejection fraction (LVEF), a measure of heart function, over baseline, as measured by echocardiography, while the mean LVEF improved only marginally in patients enrolled in the control group. This difference in LVEF between the C-Cure treated and control patients was significant ( $p < 0.01$ ) suggesting that C-Cure treatment leads to heart tissue repair." Phase III trials were expected to start by the end of 2012, based on the promising phase II results.

- **Key Expert Comments:** Experts considered the need for disease-modifying HF therapies to be extremely important, but some experts who commented were skeptical about this intervention's potential efficacy until larger and longer-term trial results are reported. Experts generally agreed that this intervention might have dramatic effects on the health care system, should its efficacy be proven, because of its disease-modifying potential. Experts thought it might significantly affect costs of treating HF in the initial cost of treatment and by reducing costs of treatment over the longer term by delaying the health decline of patients with HF.
- **Potential for High Impact:** High

## **Portable Freedom Driver for In-Home Support of the Total Artificial Heart**

- **Key Facts:** The Freedom<sup>®</sup> Driver System (SynCardia Systems, Inc., Tucson, AZ) is a wearable, pneumatic, portable driver under development to enable at-home support for the temporary Total Artificial Heart [TAH-t] (SynCardia) in patients awaiting a heart transplant. The TAH-t, approved as a bridge to transplantation by FDA in October 2004, is indicated for use in cardiac-transplant-eligible patients at risk of imminent death from nonreversible biventricular failure. The TAH-t is powered by a conventional pneumatic driver system, which is a large and cumbersome device that requires patients to remain hospitalized while awaiting a donor heart. A portable driver system that might allow patients to be discharged from the hospital while awaiting a suitable donor heart would address a significant unmet need for the relatively small number of patients in this patient population. The Freedom Driver System weighs 13.5 lb and is carried in a backpack or shoulder bag. The driver is powered by two onboard batteries that can be recharged with an automobile adapter or a standard electrical outlet. As with conventional, large, hospital-based pneumatic driver systems, the Freedom driver is connected to the implantable TAH-t by a flexible pneumatic driveline that passes through the patient's skin in the left chest just below the ribs. The

driver flashes a light or sounds an alarm when the system requires the user's attention. A clinical trial of the driver is ongoing. As of April 2012, the company had reported that 30 of 43 patients receiving the TAH-t had been discharged from the hospital using the portable driver, which is the minimum number of discharges required by the clinical trial. An August 2012 press release from the company reported that an adult male, who received the TAH-t as a bridge to transplant has logged more than 400 miles hiking since he was discharged from the hospital on March 21, 2012, using the portable driver system.

- **Key Expert Comments:** Although this intervention is expected to have a significant impact on quality of life for patients and to reduce health care costs associated with lengthy hospital stays, the patient population for which this device is intended is small, which tempers its potential overall impact on the health care system. However, experts thought that shifting care from the inpatient to the outpatient setting would be an important effect of this intervention, if it is approved for marketing.
- **Potential for High Impact:** Lower end of the potential high-impact range

## Hypertension

Hypertension, or high blood pressure, affects about one-third of the adult population in the United States and has long been described as the “silent killer” because it often shows no specific symptoms. However, more pronounced symptoms are associated with severe or long-term hypertension and include severe headache, dizziness or confusion, nausea, fatigue, blurred vision, chest pain, difficulty breathing, irregular heartbeat, and blood in the urine. According to AHA, about 76.4 million people in the United States have hypertension. National health surveys from both highly industrialized and developing nations suggest that hypertension is effectively managed in only 11.2% of cases. Hypertension was the primary cause of 61,005 deaths in the United States in 2008, the most recent year for which statistics were available, according to AHA and the American Stroke Association. Experts commenting on hypertension topics identified a new approach they thought had potential for high impact that uses a device under development for treatment-resistant hypertension.

## Catheter-Based Radiofrequency Ablation (Symplicity System) Renal Denervation for Treatment-Resistant Hypertension

- **Key Facts:** Lowering high blood pressure has been associated with significantly lower rates of stroke, heart attack, and HF, and inadequately controlled hypertension remains a problem for a growing number of people. The Symplicity™ Catheter System (Medtronic) is in development to enable a physician to apply radiofrequency energy to ablate renal nerves from within the renal artery without adversely affecting other nerves in the abdomen, pelvis, or lower extremities. In clinical trials, the minimally invasive procedure has taken about 40 minutes to perform. According to the company, physicians perform the procedure in a catheterization laboratory using standard interventional techniques similar to those used for renal stent implantation. The SYMPPLICITY HTN-3, a randomized controlled, phase III trial in the United States is ongoing and recruiting participants. This study is estimated to be completed in March 2013.
- **Key Expert Comments:** Experts commenting on this intervention agreed that it has the potential to fill an important gap in treating hypertension and would likely be somewhat accepted by clinicians and patients. However, this intervention's potential impact is tempered by its lack of longer-term outcomes data and the likelihood that it would be easily incorporated into existing health care infrastructure.

- **Potential for High Impact:** Lower end of the potential high-impact range

## Valve and Structural Disorders

This section includes topics that purport to address unmet needs for certain disorders of heart valves and one disorder associated with a ventricle malformation.

Mitral regurgitation (MR) is defined broadly as a backward flow of blood from the heart's left ventricle into the left atrium during contraction. MR can be divided into two major categories: primary, or organic MR and secondary, or functional MR (FMR). FMR is associated with poor long-term survival, and its presence in patients with ischemic and dilated cardiomyopathy is an independent risk factor for cardiovascular morbidity and mortality. According to Schmitto and colleagues, research has shown that 1-year mortality is 40% for patients with severe FMR, 17% for patients with moderate FMR, and 10% for patients with mild FMR. Significant MR occurs in an estimated 1% to 2% (about 4 million) of the U.S. population. More than 250,000 cases of significant MR are diagnosed each year in the United States and about 50,000 people undergo some type of surgery for the disease, according to one manufacturer in the field.

Aortic valve stenosis is a narrowing that obstructs normal blood flow through the aortic valve, the most likely of the heart's four valves to fail because of disease. Severe, untreated aortic valve stenosis can eventually lead to HF or sudden cardiac arrest. According to researchers, in the United States, about 29% of people aged 65 years or older and 37% of people aged 75 years or older have aortic sclerosis, a precursor condition to aortic stenosis characterized by mild thickening or calcification or both of the aortic valve without restricted leaflet motion. About 1% to 2% of the population is living with a bicuspid aortic valve, a congenital defect in which the aortic valve develops two instead of three normal valve leaflets. According to Novaro (2011) half of this population will develop aortic stenosis.

Experts commenting on topics in this area identified three devices that they thought could have high impact.

## Percutaneous Annuloplasty (Carillon Mitral Contour System) for Treatment of Functional Mitral Regurgitation

- **Key Facts:** Open surgical repair of the mitral valve, known as mitral annuloplasty, is considered the gold standard treatment for MR. Percutaneous annuloplasty is a new minimally invasive surgical approach intended to achieve the same therapeutic result, using a catheter-based technique. The Carillon<sup>®</sup> Mitral Contour System<sup>™</sup> (Cardiac Dimensions, Inc., Kirkland, WA) comprises a thin, flexible, metal bridge or tether with a self-expanding anchor at each end. The device is delivered to the coronary sinus by a catheter inserted in the jugular vein at the neck. The physician places tension on the delivery catheter to reshape the mitral annulus sufficiently to reduce the degree of MR by squeezing the mitral leaflets together to close the gap that might have developed because of heart enlargement. Two international trials are ongoing, and one international trial has been completed. Results of the TITAN trial published in August 2012 reported that use of the implant produced significant clinical improvements that persisted up to 24 months in patients with FMR. The authors reported both safety and functional data from 36 patients who permanently received the device. Fifty-three patients received the device, but 17 had to have the device recaptured. Of the 36 patients who had the device permanently implanted, the authors reported, "The 30-day major adverse event rate was 1.9%. In contrast to the comparison group, the implanted cohort demonstrated significant reductions in FMR as represented by regurgitant volume ... There was a corresponding reduction in LV diastolic volume ... and systolic

volume at 12 months compared with progressive LV dilation in the comparator.” The 6-minute distance walked showed a statistically significant improvement by patients at 24 months. The device is available in the United States only under investigational device exemption status in clinical trials. The device received the Conformité Européene (CE) mark for marketing in Europe in October 2011, and the company initiated a product launch in Europe in September 2012.

- **Key Expert Comments:** Experts commenting on this intervention generally agreed that the unmet need for a less invasive alternative to surgical mitral valve repair is important. However, experts’ uncertainty about the Carillon device’s long-term safety and efficacy profiles indicate that more data are needed to determine whether this approach will fulfill its potential. Should the device be proven safe and effective, experts thought, it might reduce recovery time and hospital length of stay for patients; they also thought that the device would be readily adopted by clinicians and patients.
- **Potential for High Impact:** Moderately high

## **Transcatheter Aortic Valve Implantation (CoreValve; Sapien) for Treatment of Severe Aortic Stenosis**

- **Key Facts:** New minimally invasive approaches are making the therapeutic benefit of aortic valve replacement an option for patients with severe aortic stenosis who are not candidates for open-heart valve surgery or who are at high surgical risk if undergoing open heart surgery. One system is approved for investigational use only (CoreValve<sup>®</sup>), while another (Sapien<sup>®</sup>) was FDA approved in November 2011 for inoperable patients, and then in September 2012 for patients at high risk if they were to undergo open-heart valve replacement.

The CoreValve System (Medtronic) features a porcine pericardial tissue valve mounted in a self-expanding, hourglass-shaped, nitinol-alloy mesh frame. The bioprosthetic valve is deployed using an 18-French diameter delivery catheter with a set of disposable catheter-loading components in a procedure that lasts up to 4 hours and requires, on average, a 3–5 day hospital stay. Medtronic received an IDE designation for its CoreValve trial from FDA in October 2010, and trials are under way. The newest addition to the CoreValve System, a 23 mm valve, received the CE mark for marketing in Europe in September 2012. The company has four valve sizes (23, 26, 29, and 31 mm) to fit aortic annulus sizes from 18 mm to 29 mm. Edwards Lifesciences Corp. (Irvine, CA), developed the Sapien Transcatheter Heart Valve system, which features a bovine pericardial tissue aortic valve affixed within a balloon-expandable, cobalt-chromium alloy frame. The bioprosthetic valve is available in 23 and 26 mm lengths. The company has developed delivery systems for implanting the valve using either a transfemoral or transapical approach. The procedure takes up to 4 hours, including about half an hour for fluoroscopy, with an average hospital stay of 2–6 days. In November 2011, FDA approved the Sapien for transfemoral delivery for treating severe, symptomatic, aortic stenosis in patients who have been determined by two cardiac surgeons to be ineligible for open aortic valve replacement and in whom existing comorbidities would not preclude the expected benefit from the procedure. In October 2012, FDA expanded the labeling to include patients with severe aortic stenosis who are at high risk of experiencing surgical complications. FDA requested, as a condition of the initial 2011 approval, two substantial postapproval studies. One study will conduct long-term followup on patients already enrolled in the pivotal PARTNER trial, and the second study will track new U.S. patients given the valve in a registry. In May 2012, CMS released a national coverage

determination stating that CMS “covers transcatheter aortic valve replacement (TAVR) under Coverage with Evidence Development (CED)” when the procedure is used for “the treatment of symptomatic aortic valve stenosis when furnished according to an FDA approved indication” and when numerous conditions are met, including the required credentials and experience of the facilities and surgeons who perform the procedure.

The Sapien valve device costs a reported \$32,500. In November 2011, investigators reported a cost-effectiveness comparison between TAVR, also known as transcatheter aortic valve implantation (TAVI), and open-heart aortic valve replacement among Cohort A (high-risk) patients in the PARTNER trial. The authors found that for transfemoral TAVI, procedural costs were substantially higher than those for open-heart aortic valve replacement. However, overall treatment costs for the entire index hospitalization were \$2,500 lower for transfemoral TAVI than for open surgery, largely because of a shorter TAVI hospital stay.

The technology requires significant and costly infrastructure investments (hybrid operating room costing \$3 million to \$4 million); a new type of interdisciplinary cardiac care team in which the interventionalist and surgeon work together with technologists, cardiac nurses, anesthesiologist; a special recovery room; the ability to convert to open surgery if needed; and extensive training of the entire team.

- **Key Expert Comments:** Experts commenting on this intervention agreed that it would offer an important and effective new treatment modality for patients who have no other medical or surgical treatment option. Experts thought that this intervention would improve patient health outcomes and that an increase in patient volume and a shift in care setting (from outpatient to inpatient) would occur as this intervention diffuses. Experts opinions diverged about whether and how much this intervention would disrupt health care infrastructure, but agreed that the intervention has the potential to both increase (in the short term) and decrease (in the long term) health care costs associated with this patient population.
- **Potential for High Impact:** High

## **Transcatheter Mitral Valve Repair (MitraClip) for Treatment of Mitral Regurgitation**

- **Key Facts:** Transcatheter mitral valve repair with the MitraClip® device (Abbott Laboratories, Abbott Park, IL) is intended to simulate the functional effects achieved by the standard open-surgery repair procedure used for treating MR. In the standard procedure, a surgeon sutures together the edges of the two opposing mitral valve leaflets at the center of the valve opening, leaving two smaller openings on either side that close more completely than a single large opening. In a MitraClip procedure, the physician uses a transcatheter approach in which a two-armed, flexible metal clip covered in polyester fabric is used, rather than the sutures used during open surgery. Researchers reported 3-year followup of 258 patients from the EVEREST II randomized controlled trial. They reported a freedom-from-mortality rate of 87% for MitraClip patients compared with 85% for surgery patients, and a freedom-from-surgery rate of 78% for MitraClip patients compared to a freedom-from-resurgery rate of 96% for surgery patients. The device is in phase III trials in the United States. It received the CE mark for marketing in Europe in 2008 for use as a nonsurgical option in patients with severe MR.
- **Key Expert Comments:** Overall, experts commenting on this technology agreed this procedure addresses a considerable unmet need and has the potential to improve patient health, although some experts agreed more data concerning safety and long-term outcomes



are needed. Experts were split on whether this technology would disrupt health care delivery. Some experts believe that there would be little disruption to health care delivery because the infrastructure is already in place, while other experts believe that the increase in patient volume might cause a large disruption to health care delivery. The majority of experts believe the MitraClip would increase health care costs, but more long-term data are needed to determine whether it would decrease long-term costs by reducing the need for standard therapy for this population.

- **Potential for High Impact:** High

# **Arrhythmia Interventions**

## **Cardiac Pacing System (Revo) for Patients Who May Require Future Magnetic Resonance Imaging**

As the use of cardiac pacemakers has grown, so too has the use of magnetic resonance imaging (MRI) for various clinical indications. However, the strong magnetic fields produced by MRI are known to pose potential risks to patients with implanted pacemakers, which contain metal components. MRI scanner effects on implanted cardiac devices can include electrode-tip heating, migration or movement of the device, malfunction or damage of the device, and changes in pacing thresholds.<sup>1</sup> MRI technologists have attempted to modify imaging sequences to avoid complications in patients with implanted pacemakers, but many clinicians as well as patients are unwilling to risk MRI. To address concerns about pacemaker-compatible MRI imaging, one company has developed a new pacemaker, which the U.S. Food and Drug Administration (FDA) approved in February 2011. The Revo MRI™ SureScan® pacing system (Medtronic, Inc., Minneapolis, MN) is a dual-lead, electronic, implantable cardiac pacemaker engineered to allow patients to safely undergo MRI scans under specific conditions. The complete system includes the Revo MRI SureScan IPG (implantable pulse generator) and two CapSureFix® MRI SureScan leads for use in an MRI environment. The pacemaker is approved as “MR-conditional,” meaning it can be used in an MRI environment under certain conditions according to the type of MRI scanner and scanner settings.<sup>2-4</sup>

In 2011, Wilkoff and colleagues reported results from a phase III controlled trial of 464 patients with bradycardia who had Revo pacemakers; 258 patients underwent MRI, and 206 control patients had no MRI. No MRI-related complications—including sustained ventricular arrhythmias, pacemaker inhibition or output failures, electrical resets, or other pacemaker malfunctions—occurred during or after MRI procedures. Pacing capture threshold and sensed electrogram amplitude changes were minimal and similar between study groups.<sup>5</sup>

The list price for the Revo is \$13,000, according to Medtronic,<sup>6</sup> and is covered by Medicare for approved conditions.<sup>7</sup> In July 2011, the U.S. Centers for Medicare & Medicaid Services (CMS) issued a final decision memorandum regarding MRI scans in patients who have received an FDA-approved MRI-compatible pacemaker under certain conditions. In the memorandum, CMS stated “[MRI] improves health outcomes for Medicare beneficiaries with implanted permanent pacemakers (PMs) when the PMs are used according to the FDA-approved labeling for use in an MRI environment... . Other contraindications that may be present in any given beneficiary would continue to apply in patients with PMs.”<sup>8</sup>

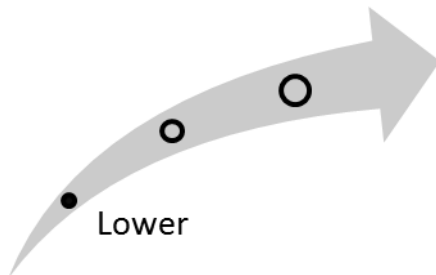
## **Clinical Pathway at Point of This Intervention**

Cardiologists recommend implanting an electronic cardiac pacemaker for a number of conditions that create various heart rhythm abnormalities. Clinical guidelines recommend implantation of cardiac pacemakers for several indications (with various subcategories within each broad indication), including acquired atrioventricular block in adults, atrioventricular block associated with acute myocardial infarction, chronic bifascicular block, hypersensitive carotid sinus syndrome, hypertrophic cardiomyopathy, neurocardiogenic syncope, and sinus node dysfunction. Permanent pacemaker implantation is recommended in children, adolescents, and adults with certain congenital heart defects. Certain patients who undergo heart transplantation might require permanent pacemaker implantation to treat bradycardia (slow heartbeat). Patients with certain neuromuscular disorders, such as myotonic dystrophy and Emery-Dreifuss muscular dystrophy, might require pacemaker implantation.<sup>9</sup>

The strong magnetic fields produced by MRI pose a risk to patients with implanted cardiac pacemakers, which contain metal components. These MRI-related device problems can cause

arrhythmia or death. Thus, current clinical guidelines discourage the use of cardiovascular MRI in patients with implanted pacemakers. The exception would be when cardiovascular MRI is performed at highly experienced centers in cases with a strong clinical indication and when the potential benefits of cardiovascular MRI significantly outweigh the potential risks of the procedure.<sup>10</sup> The dual-lead Revo MRI SureScan pacing system would be used in place of conventional, non-MRI-safe, dual-chamber, cardiac pacemakers for the same types of clinical indications.

**Figure 1. Overall high-impact potential: cardiac pacing system (Revo) for patients who may require future magnetic resonance imaging**



Experts commenting on this new device were divided about its potential impact. On one hand, experts agreed that being able to conduct MRI scans in patients with pacemakers is important. However, novel protocols are being investigated to determine whether conventional pacemakers can be used in this capacity, which could obviate the need for the Revo. Although experts thought acceptance of the device would be high for both clinicians and patients, costs, training requirements, and lack of pacing-efficacy and safety data might temper its diffusion. Based on this input, our overall assessment is that this intervention is in the lower end of the high-potential-impact range.

## Results and Discussion of Comments

Seven experts, with clinical, research, health systems, and health administration backgrounds, commented on this intervention.<sup>11-17</sup>

According to experts, the primary advance this device offers is expanding the patient population (to include those who have a pacemaker) that will be eligible for MRIs. Experts purport that this unmet need is important, given the valuable diagnostic information that MRIs provide and the number of patients with pacemakers. As one expert pointed out, “In radiology, CT [computed tomography] cannot substitute for MRI in some cases. For example, the soft tissue contrast in the peripheral joints is much greater with MRI than CT, and as such patients with a pacemaker who need an MRI would greatly benefit from this intervention.”<sup>11</sup> Another expert, with a background in cardiology, stated, “Clearly, MRI has become a critical diagnostic test for a number of diseases in almost every organ system” and that “the potential adverse events that might occur when MRI is applied to patient with cardiovascular implantable endovascular devices (CIED) has been seen as a major disadvantage to the use of the [CIEDs].”<sup>12</sup> However, this same expert noted that some medical institutions (e.g., Johns Hopkins University and Hospital, Baltimore, MD) have conducted research that suggests that “MRI may be applied safely to most patients with a currently manufactured CIED with only a few precautions.”<sup>12</sup>

Experts agreed less on whether this intervention will improve patient health outcomes. Although several experts noted that the ability to use MRI in these patients might improve treatment decisions and diagnostic practices, others noted that the device itself does not have a direct therapeutic benefit. Despite these observations, experts generally agreed that most clinicians and patients would

readily accept the technology, provided that the training involved and the technology costs are manageable. However, a couple of experts pointed out potential barriers to clinical acceptance of this technology. One expert noted that the Revo, although MRI-compatible, does not have all the capabilities that other CIEDs on the market have, potentially prompting physicians to choose a different pacemaker. Several experts noted that clinicians would likely prefer to have longer-term data on the pacing efficacy and safety of the Revo device. More than one expert noted that this device would require new MRI scanning protocols and that the care team would need to be extensively trained on these.

Experts thought that this technology would have a measurable impact on health care costs. First, several experts noted that the cost of the Revo was higher than costs of other pacemakers. Second, experts thought that costs will also rise as the number of MRI scans performed increases.

## **Subcutaneous Implantable Cardioverter-Defibrillator (S-ICD) for Treatment of Life-Threatening Ventricular Tachyarrhythmias**

The use of implantable cardioverter-defibrillators (ICDs) is an established therapy to prevent sudden cardiac arrest (SCA) from ventricular arrhythmias. Conventional ICDs have a transvenous lead that is placed in the heart for cardiac sensing and defibrillation.<sup>18</sup> This transvenous lead, however, can cause serious complications, both during and after implantation. Complications such as cardiac tamponade, pneumothorax, and hemothorax can occur during the lead implantation, and lead failure can occur after implantation, which is a major limitation of this therapy.<sup>18</sup> Lead failure can generate unnecessary shocks or fail to provide necessary shocks. Removal of faulty leads is often associated with morbidity and mortality. Lead problems, occurring in an estimated 40% of cases, have prompted development of a leads-free ICD system.<sup>18</sup>

The Subcutaneous Implantable Cardioverter-Defibrillator (S-ICD<sup>®</sup> System, Boston Scientific Corp., Natick, MA) was FDA approved in September 2012 “to provide defibrillation therapy for the treatment of life-threatening ventricular tachyarrhythmias in patients who do not have symptomatic bradycardia, incessant ventricular tachycardia, or spontaneous, frequently recurring ventricular tachycardia that is reliably terminated with anti-tachycardia pacing.”<sup>19</sup> The S-ICD System components consist of the SQ-RX<sup>®</sup> pulse generator, the Q-Trak<sup>®</sup> subcutaneous electrode, the Q-Guide<sup>™</sup> electrode insertion tool, and the Q-Tech<sup>™</sup> programming system.<sup>20</sup>

The S-ICD can typically be implanted during an outpatient procedure and uses a subcutaneous electrode rather than transvenous leads to both sense the need for and deliver therapy. Furthermore, the device does not require use of fluoroscopy or imaging equipment for placement because the system components are designed to be positioned using only anatomic landmarks. The ICD and its lead are placed subcutaneously in the left thoracic region around the fifth and sixth intercostal spaces at the mid-axillary line. The lead with its wire runs laterally from the ICD to the xiphoid, then vertically along the left lateral sternal margin.<sup>19,21,22</sup>

The battery-powered, computer-controlled pulse generator is intended to detect cardiac activity and provide defibrillation; the manufacturer states that the battery lasts 5.1 years.<sup>20</sup> The subcutaneous electrode enables cardiac activity to be sensed by the pulse generator and delivers defibrillation energy, provided by the pulse generator, to the heart.<sup>20,22</sup> The external programmer is designed to allow clinicians to set parameters for the pulse generator and retrieve data.<sup>23</sup>

In a clinical trial of 64 patients in whom either the S-ICD system or single- (SC-TV) and dual-chamber (DC-TV) transvenous ICD system were implanted, authors concluded, “Appropriate detection of ventricular tachyarrhythmias for subcutaneous and TV devices in single- and dual-zone configurations was 100% and >99%, respectively. Specificity for supraventricular arrhythmias was significantly better for the S-ICD system compared to 2 of 3 TV systems, as well as the composite of TV devices (98.0% [S-ICD] vs 76.7% [SC-TV range: 64.0-92.0%] vs 68.0% [DC-TV range: 32.7-89.8%;  $P < 0.001$ ]).”<sup>24</sup>

An international registry, the EFFORTLESS registry, is collecting data on S-ICD use, and it included implant test data from 219 patients as of a June 2012 report from the CardioStim conference in Nice, France.<sup>25</sup> Cardiologist Lucas Boersma reported that the device worked on the first test try in 216 patients, and 19 discrete ventricular tachycardia (VT) or ventricular fibrillation (VF) episodes have been reported in 14 patients. As in the study completed for the premarket approval application, the rate of successful spontaneous conversion of VT or VF was reported as 100%. Two episodes converted late after one shock, and three episodes needed several shocks to convert successfully; two patients experienced a VT storm but were successfully treated.<sup>25</sup>

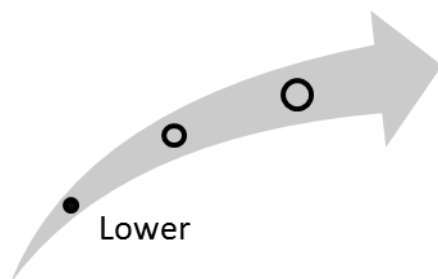
The S-ICD system, developed by Cameron Health, Inc. (San Clemente, CA), is produced by Boston Scientific following its acquisition of Cameron Health in 2012. The device received the CE mark in 2009 for distribution in Europe.<sup>26</sup> Boston Scientific planned a phased launch of the system in the United States to ensure that clinicians are trained to use the system in a safe and effective way.<sup>19</sup> As of September 2012, the company stated that more than 1,400 S-ICD systems had been implanted in patients around the world.<sup>19</sup> The cost of the device is reported to be similar to costs of conventional ICDs; however, the procedure may take less time to perform because it can be performed in an outpatient setting with no need for fluoroscopy or an electrophysiology laboratory.<sup>27</sup>

CMS's national coverage determination on ICDs does not mention the S-ICD specifically, but ICDs that are FDA approved are covered as medically necessary when a beneficiary meets certain eligibility criteria.<sup>28</sup> Some private, third-party payers have updated their ICD policies to include the S-ICD device (with conditions).<sup>29,30</sup> and others have not yet updated their policies yet and continue to list the S-ICD as "experimental/investigational" and without approval, although it has FDA approval.<sup>31</sup>

## Clinical Pathway at Point of This Intervention

According to the American College of Cardiology (ACC) and the American Heart Association (AHA), prophylactic ICDs are the preferred treatment for patients with VF who are at risk of SCA. For patients who do not meet criteria for an ICD, beta blockers are considered first-line therapy, and radiofrequency ablation might be indicated. For patients with VF refractory to ICD, drug therapy and radiofrequency catheter ablation or antiarrhythmic surgery might be warranted.<sup>32</sup> The S-ICD system competes directly with standard ICD systems that require a transvenous electrode in the heart. Clinicians might prefer the S-ICD System to other ICD systems because it offers the potential to reduce procedure-related complications and lead-related adverse events, and it does not require imaging during placement.

**Figure 2. Overall high-impact potential: Subcutaneous Implantable Cardioverter-Defibrillator (S-ICD) for treatment of life-threatening ventricular tachyarrhythmias**



Overall, experts commenting on this topic expressed that this intervention might have some potential to improve patient health outcomes by reducing complications associated with lead-based ICDs and associated secondary surgeries that carry a high risk of morbidity and some mortality. Because the implantation procedure requires fewer resources and can be performed in an outpatient setting, this intervention could shift care delivery to a less invasive setting and bring about shorter hospital stays. However, some experts suggested that this device's limited capabilities, compared with other ICDs, might temper its diffusion. Based on this input, our overall assessment is that this intervention is in the lower end of the high-potential-impact range.

## Results and Discussion of Comments

Six experts, with clinical, research, health systems, and health administration backgrounds, commented on this intervention.<sup>33-38</sup> One of these experts declared a potential conflict of interest because the expert is a electrophysiologist who acts as a consultant to Cameron Health and was an investigator in the S-ICD IDE study.<sup>35</sup> This potential conflict of interest is balanced by the perspectives of other experts who did not declare conflicts of interest.

Experts generally agreed that the unmet need this intervention is purporting to address is important, based on both the “high incidence of lead failure in conventional ICDs and the high morbidity and mortality associated with lead failure and replacement in these devices.”<sup>33</sup> Most experts thought that this intervention has the potential to meet this need, although a few experts suggested that longer-term data will be necessary before clinicians will fully adopt the technology and that this device’s diffusion might be limited by its limited pacing capabilities. One expert, speaking from a clinical perspective, stated: “The main advantage of the system is its degree of invasiveness, which is much less [than currently available ICDs]. However, there are substantial weaknesses with a device that does not have a lead ... does not advocate [its] ability to [conduct] event tachycardia pacing or bradycardia pacing ... with a device that is large and placed in the axilla.”<sup>37</sup>

Experts generally thought that the S-ICD would improve patient outcomes, partly because of the theory underlying the technology, but also because of the data collected thus far.

Because ICD placements are common, this intervention is unlikely to significantly disrupt current care models or operations processes, with a few exceptions, experts noted. First, because the device is leadless and can be placed using only anatomic landmarks, specialized cardiac procedure rooms and fluoroscopy/imaging might be used less, the experts commented. Experts commenting also noted that the device can be implanted in an outpatient setting, which would shift care from the inpatient to outpatient setting that is associated with available ICDs. They also noted that surgeons implanting the device might require some initial S-ICD-specific training.

Although the S-ICD cost is similar to that of other ICD systems, experts thought that this intervention has the potential to reduce some financial burden by avoiding lead complications and shifting the setting from inpatient to outpatient surgery. Experts agreed that both patients and clinicians would likely adopt this device if it is effective relative to existing ICDs, although several experts commented on the need for longer-term data if this is to occur.



## **Brain Aneurysm Intervention**

## Endovascular Pipeline Embolization Device (PED) for Treatment of Giant and Wide-Necked Intracranial Aneurysms

A brain aneurysm or intracranial aneurysm (ICA) is a bulging or balloon-like enlargement of a blood vessel in the brain that occurs from a weakening of the vessel wall.<sup>39,40</sup> Aneurysms are typically classified by size (small, medium, large, and giant) and shape (saccular, saccular with a wide neck, or fusiform). These characteristics and the aneurysm location can influence the risk of aneurysm rupture.<sup>41</sup> Aneurysm rupture can lead to subarachnoid hemorrhage, brain damage, stroke, and death. About 40% of aneurysm ruptures are fatal, and 66% of patients who survive the rupture live with a permanent neurologic deficit. The Brain Aneurysm Foundation reports that ICAs occur in about 1 in 50 people, and an estimated 8–10 brain aneurysm ruptures per 100,000 people occur annually.<sup>42</sup>

Patients with giant or large wide-necked aneurysm face limited treatment options; standard therapy is often complicated for these aneurysms. In this subset of ICAs, clinicians often need to use adjunctive devices during treatment, complications associated with treatment are high, and complete treatment cannot always be accomplished. When treatment is accomplished, it is often not successful at preventing recurrence; recurrence rates are about 50%.<sup>43</sup>

The Pipeline<sup>®</sup> Embolization Device (PED, Covidien, plc, Dublin, Ireland) is a new therapeutic option specifically for these difficult-to-treat aneurysms. The PED is a flow-diversion device that FDA approved in April 2011 for endovascular treatment of adults with large or giant wide-necked brain aneurysms of the internal carotid artery.<sup>44</sup> The device is a braided, cylindrical, mesh implant designed to block blood flow to the aneurysm while restoring natural blood flow in the affected artery. The device is implanted using endovascular techniques; therefore, it does not require open surgery. Once the neurovascular surgeon delivers the PED via catheter to the aneurysm, the PED is positioned across the aneurysm neck and expanded against the vessel walls to block blood flow to the aneurysm. The company states that once in place, the PED causes remodeling of the parent artery by providing a scaffold that eventually becomes endothelialized, creating a “permanent biological seal” across the aneurysm. The aneurysm is then excluded from the natural circulation, and natural blood flow in the artery is restored. This occlusion causes the remaining blood in the aneurysm to clot, and the aneurysm shrinks.<sup>45</sup>

According to a report from the manufacturer, four clinical trials reported a 0% rate of aneurysm recurrence following PED treatment. The aneurysm occlusion rates reported in the manufacturer’s summary of these trials ranged from 85.7% to 94% at 1-year post-treatment.<sup>45</sup> The rate of stroke or death following treatment in these trials was reported as 0% to 6.5%.<sup>45</sup> An early postmarket multicenter study of 56 patients reported a major complication rate of 8.5% and indicated the complication rate was significantly associated with ICAs in the vertebrobasilar system.<sup>46</sup> Another postmarket study involving 34 patients with 41 ICAs reported immediate flow disruption in 97% of treated aneurysms, with major complications, defined as a major stroke or death, in 3% of the treated patients. Other complications occurring in 12% of these patients included minor stroke, cerebral nerve palsy, transient neurologic deficit, and groin complications.<sup>47</sup>

The PED, originally developed by Chestnut Medical Technologies, Inc. (Menlo Park, CA), is manufactured by ev3 Endovascular, Inc. (Plymouth, MN), a company that Covidien acquired in 2010.<sup>48</sup> The PED is delivered by the same care team that treats aneurysms using endovascular stent coiling. A company spokesperson stated that the training program for the device involves a day and a half of “physician benchtop didactic training,” then five FDA-required physician-proctored cases and five FDA-required additional proctored cases.<sup>49</sup>

Neurovascular surgeons from Johns Hopkins University published a cost-comparison report in November 2012 in the journal *Neurosurgery* based on 60 consecutive cases at Johns Hopkins in which the PED was used (n=30; average aneurysm size 9.8 mm) and traditional stent coiling was used (n=30; average aneurysm size 7.3 mm). They reported, “The total combined costs of proximal access/guide catheters, microcatheters, and microwires were equivalent between the 2 groups. The cost of implants, however, was significantly lower in the PED group (\$13 175 ± 726 vs \$19 069 ± 2015; p = .013), despite this group having a larger mean aneurysm size. Furthermore, the total procedure cost was significantly lower for the PED group vs the stent-coiling group (\$16 445 ± 735 vs \$22 145 ± 2022; p = .02), a 25.7% cost reduction. This represents a 27.1% reduction in the cost per millimeter of aneurysm treated in the PED group (\$2261 ± 299) vs the stent-coiling group (\$3102 ± 193; p = .02).”<sup>50</sup>

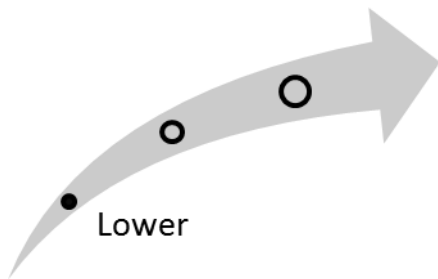
The device appears to have received generally broad clinical acceptance since its FDA approval, with many U.S. neurovascular centers announcing its availability.<sup>51-55</sup> For example, neurosurgeons at the Mayo Clinic reported in April 2012 that since PED’s introduction in their neurovascular service line, more than 20% (38/175) of unruptured aneurysms (mean size 8.5±6.1 mm) at their institution were treated with the PED. Some indicate that diffusion is progressing to include other types of aneurysms, including smaller (than wide necked or giant) aneurysms,<sup>56</sup> and ruptured aneurysms.<sup>56</sup> The wide diffusion indicates that third-party payers are generally covering use of the device for FDA-approved indications for treating intracranial aneurysms. We identified only one payer policy specifically mentioning the device.<sup>29</sup> CMS has no national coverage determination; thus, coverage is left to the discretion of local carriers.

## **Clinical Pathway at Point of This Intervention**

The choice of treatment for unruptured ICAs is based on size, shape, and location of the aneurysm, as well as the patient symptoms, health, age, and family history.<sup>41,57</sup> Small aneurysms usually have a low risk of rupture and, if they are not causing symptoms, typically require only routine monitoring by imaging the aneurysm size, taking blood pressure, and recording any other symptoms. In patients who have risk factors for aneurysm rupture, or who have an aneurysm that produces symptoms, surgical or endovascular management is indicated, depending on size, shape, and location of the aneurysm and the patient’s risk factors.<sup>41</sup> Typical surgical management involves opening the skull, isolating the affected artery in the brain, and placing a surgical clip at the base of the aneurysm.<sup>41</sup> Other surgical management involves vascular bypass of the affected vessel segment.<sup>58</sup> In common endovascular management, clinicians use an endovascular coiling procedure, a minimally invasive embolization procedure that involves delivering platinum micro-coils to the aneurysm via a microcatheter and imaging guidance. The microcoils are placed in the aneurysm to embolize, or seal off, the aneurysm.<sup>41,59</sup> Delivering liquid embolic agents that act like a glue in the aneurysm is a newer endovascular embolization technique that may also be used to treat the aneurysm.<sup>60</sup> Endovascular embolization of large or wide-necked aneurysms typically requires adjunctive therapy such intracranial stents or balloons to hold the coils or liquid embolic agent in place.<sup>40,60</sup>

The PED may provide a safer, more efficacious treatment option for patients with large or giant wide-necked ICAs. The PED may also allow treatment of patients whose giant or wide-necked aneurysms have characteristics that preclude them from treatment.<sup>40</sup>

**Figure 3. Overall high-impact potential: endovascular Pipeline Embolization Device (PED) for treatment of giant and wide-necked intracranial aneurysms**



Although some experts thought that the subset of patients this device intends to treat is small, all experts agreed that these patients have limited treatment options, and the PED fulfills an unmet need for these patients. Experts believe the PED has the potential to improve patient health by decreasing the rate of aneurysm recurrence and lowering the risk of aneurysm rupture and procedure-related complications. Because treating ICAs with the PED device is less invasive and is purported to result in fewer procedural complications, most experts believe this device would be widely accepted by clinicians and patients, although some experts thought the technical difficulty and learning curve of the procedure along with the required proctoring before clinical use will somewhat temper diffusion. Based on this input, our overall assessment is that this intervention is in the lower end of the high-potential-impact range.

## Results and Discussion of Comments

Seven experts with clinical research, and health systems background, offered perspectives on this intervention.<sup>61-67</sup> The experts agreed that an unmet need exists for treating large and giant wide-necked ICAs because of limited treatment options, poor treatment results, high risks for aneurysm recurrence, and the clinical consequences of a ruptured aneurysm. All experts agreed that the PED could play an important role in addressing this unmet need. The PED, experts believe, has a high potential to improve patient health by reducing the risk of aneurysm recurrence and rupture and by decreasing the adverse-event rates associated with current treatment. Some experts had some concern regarding lack of long-term efficacy data, but agreed that the current clinical trial indicates that the PED is safe and efficacious in treating large and giant wide-necked aneurysms at least in the short term. Two experts expressed some concern regarding the potential for the PED to block important small side branch vessels and suggested more research would be necessary to clarify those risks.

The PED is delivered by endovascular technique, a minimally invasive technique, and several experts noted that this could decrease the length of hospital stay for patients who would have previously been candidates for open craniotomy and provide a treatment option for patients who are considered surgical risks. This, paired with the potential for less procedural complications, could affect the current health care delivery infrastructure and how patients are currently managed. Overall, experts thought that because the health care delivery infrastructure for performing catheter-based techniques to treat aneurysms is already in place, the PED procedure would have minimal effect on the infrastructure.

The PED's cost was thought to be high by most experts, although it was considered to be lower or close in comparison to alternative procedures. Regardless of costs, the majority of experts believe that the PED has minimal to moderate potential to decrease overall health care costs down the line by preventing or decreasing aneurysm-related complications and resultant disability, reducing aneurysm recurrences, and by reducing length of hospital stay. One expert noted that because the

population of patients that this procedure is intended for is small, the effects on overall costs would not be that great.

Experts thought that the PED would be moderately to widely adopted by clinicians as a new device to treat ICAs because it involves a minimally invasive procedure. The minimally invasive treatment also makes it attractive to patients, according to the experts. They believe that this fact and its potential to be safer and more effective than existing options, would generate acceptance by patients with ICAs who need treatment. Basing their opinions on the fact that PED therapy is an endovascular procedure, most experts believe that PED delivery should be a relatively easy procedure to learn for physicians already performing endovascular techniques. One expert noted, however, that PED delivery is somewhat more difficult than endovascular coiling or stenting, and the learning curve will be longer for physicians. Because of this and the training requirements, this expert thought that clinician acceptance might be somewhat tempered. Another expert believes that clinicians would not readily adopt the procedure until sufficient data are available regarding the PED's longer-term performance.

## **Heart Failure Interventions**

## **Autologous Mesenchymal Stem Cell Therapy (C-Cure) for Heart Failure**

First-line treatments for heart failure (HF) are typically palliative and address only disease symptoms rather than the underlying loss of cardiomyocytes, which is HF's hallmark.<sup>68</sup> In light of this, stem cells have been investigated to improve the heart's capacity for self-repair.<sup>68</sup> In early clinical trials, first-generation, "undifferentiated" stem-cell therapies for HF have shown limited clinical benefit. Therefore, researchers are now suggesting pretreating cells with "activators" designed to improve the cells' cardiac homing ability and possible survival in cardiac tissue.<sup>69</sup>

C-Cure<sup>®</sup> also known as C3BS-CQR-1 (Cardio3 Biosciences, S.A., Mont-Saint-Guibert, Belgium), is a bone-marrow-derived, cardiopoietic, autologous mesenchymal stem cell (MSC) therapy that is being investigated for treating HF.<sup>70</sup> The therapy involves harvesting MSCs from the patient's bone marrow, treating the cells with growth factors ("cardiopoietic cocktail"), and injecting the cells into the patient's heart.<sup>70</sup> The cocktail includes transforming growth factor-beta1, bone morphogenetic protein-4, activin A, retinoic acid, insulin-like growth factor-1, fibroblast growth factor-2, alpha-thrombin, and interleukin-6.<sup>71</sup> The company claims that treatment with these proteins can transform MSCs (which are undifferentiated) into cardiac progenitor cells to replicate natural cardiogenesis without modifying the cell's genome.<sup>70,72</sup> The cardiac progenitor cells are designed to behave identically to cells lost during progression of HF, and they potentially regenerate damaged heart muscle without risk of rejection.<sup>73</sup>

In clinical trials, stem cells have been initially collected from the patient's iliac crest. After cells are treated ex vivo, they are administered into the patient's left ventricle via 20 endomyocardial injections at sites bordering the damaged heart tissue. According to the company, this process takes place during a single surgical procedure, and cardiac electromechanical mapping is used to identify injection sites.<sup>71,72</sup>

According to an April 2011 company press release, researchers reporting on a phase II trial of 45 patients in Belgium and Serbia with severe HF of ischemic origin who were treated with optimal standard of care or optimal standard of care plus C-Cure concluded, "Patients receiving C-Cure saw an 18.1% increase in left ventricular ejection fraction (LVEF), a measure of heart function, over baseline, as measured by echocardiography, while the mean LVEF improved only marginally in patients enrolled in the control group. This difference in LVEF between the C-Cure treated and control patients was significant ( $p < 0.01$ ) suggesting that C-Cure treatment leads to heart tissue repair."<sup>74</sup> In September 2011, the company reported that it planned to discuss the phase II results with FDA and the European Medicines Agency before finalizing the protocol for phase III trials.<sup>75</sup> The company had planned to begin a large, phase III trial at European and U.S. centers by the end of 2011 to support applications for marketing in Europe and the United States; however, the company's Web site indicates a plan to start a phase III trial in 2012; however, as of October 2012, the trial had not been registered on the National Clinical Trials database.<sup>70,71,76</sup> In September 2011, Cardio3 announced that it had established a subsidiary in Rochester, MN, to support the expansion of the company's clinical and regulatory activities in the United States.<sup>75</sup>

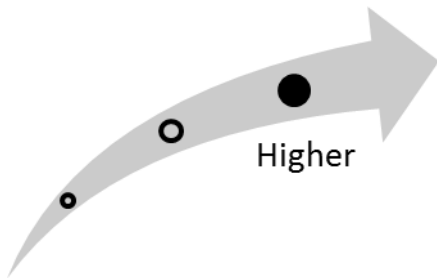
### **Clinical Pathway at Point of This Intervention**

In general, first-line medical HF management includes angiotensin-converting enzyme inhibitors and beta blockers, with the option of adding angiotensin receptor blockers, digoxin, diuretics, or aldosterone antagonists to the treatment regimen for certain subpopulations.<sup>77,78</sup> In some cases, surgical intervention (e.g., coronary bypass surgery, heart valve repair or replacement, ventricular-assist device implantation) may be indicated. Patients with severe HF may require a

heart transplant.<sup>78</sup> If approved by FDA for marketing in the United States, C-Cure stem cell therapy would likely be positioned as the first regenerative therapy available for patients with HF.

This stem cell therapy may reduce the need for pharmacotherapies that address symptoms of HF. However, it should be noted that in clinical trials investigating the use of guided stem cell therapy, patients receiving the intervention remained on a regimen of standard-of-care medical therapy. Thus, the company may intend the stem cell therapy to be used in conjunction with standard medical therapy. If approved for marketing, the stem cell therapy also has the potential to displace some of the need for other surgical interventions used as HF advances. The lifestyle changes (e.g., diet, exercise) that often accompany HF treatment would likely remain complementary interventions to stem cell therapy.

**Figure 4. Overall high-impact potential: autologous mesenchymal stem cell therapy (C-Cure) for heart failure**



Although some experts commenting on this procedure were skeptical about this intervention's potential efficacy until they see results from larger and longer-term trials, they generally agreed that this intervention may have dramatic effects on the health care system, should its efficacy be proven. Furthermore, experts consider the need for disease-modifying HF therapies to be extremely important. As a potentially disease-modifying therapy for HF, experts commented, this therapy has the potential to significantly affect certain parameters of the health care system, including increasing the initial cost associated with treating HF and establishing a treatment paradigm that treats the disease instead of the disease's symptoms. Based on this input, our overall assessment is that this intervention is in the higher end of the high-potential-impact range.

## Results and Discussion of Comments

Six experts, with clinical, research, health administration, and health systems backgrounds, provided perspectives on this topic.<sup>79-84</sup> The experts strongly agreed that the need for disease-modifying treatments for HF is extremely important, given the high prevalence of the disease, the inability of current treatments to reverse or slow its progression, and its associated mortality and decreased quality of life for patients. In general, experts were optimistic about this intervention's potential to meet this need, based on both available trial data and the scientific theory underlying the intervention. One research-based expert, with expertise in the field of regenerative medicine, stated: "C-Cure has a great potential to improve patient health as the preliminary results from clinical trials were very promising, not only showing great safety but also significant improvements in heart function. These results are supported by numerous studies of mesenchymal stem cells improving cardiac function and recovery after infarct or other heart damage."<sup>84</sup> However, more than one expert noted that results from longer-term, larger trials are needed before any definitive predictions can be made about the intervention's efficacy. An expert with a background in cardiology stated, "Many promises with stem cell therapy so far have not been fulfilled."<sup>81</sup>

Experts generally asserted that, if effective, this treatment has the potential to disrupt health care processes. First, the focus of care would shift to regeneration and the underlying cause of HF, rather



than on treating symptoms. Second, experts indicated if this intervention is proven effective, it has the potential to obviate the need for expensive interventions (e.g., coronary bypass, heart transplantation) for patients with late-stage HF. Third, experts often commented that this treatment requires a surgical procedure during a stage of HF that has previously been treated only with pharmacotherapy. Some experts noted the infrastructure changes that this intervention would necessitate, such as expansion of facilities and care teams. However, some experts noted that despite these initial changes, the intervention might obviate the need for other, invasive procedures or pharmacotherapy, thereby reducing demand for care over time.

Experts agreed that this procedure would be likely to be very expensive initially, based on the costs of the stem cell harvesting and treatment and the surgical injection procedure, but that it could reduce costs over time, especially if HF progression is reversed and, in turn, the need for additional HF interventions is obviated. Some experts thought that these costs would be prohibitively high for patients, especially in the absence of insurance coverage. Although experts generally thought that most patients and clinicians would accept this procedure, given the lack of other disease-modifying treatments for HF, several suggested that the invasiveness of the procedures involved in this therapy would pose a barrier to acceptance for some patients.

## **Portable Freedom Driver for In-Home Support of the Total Artificial Heart**

The temporary Total Artificial Heart (TAH-t, SynCardia Systems, Inc., Tucson, AZ), is a biventricular, implantable device that functions in place of the two failing ventricles and four valves of a failing heart by pumping blood to both the pulmonary and systemic circulations via an external pneumatic driver.<sup>85,86</sup> The TAH-t, approved as a bridge to transplant by FDA in October 2004,<sup>87</sup> is indicated for use “in cardiac-transplant-eligible patients at risk of imminent death from nonreversible biventricular failure.”<sup>88</sup> The TAH-t is powered by a conventional pneumatic driver system, which is a large and cumbersome device that requires patients to remain hospitalized while awaiting a donor heart.<sup>89</sup> A portable driver system that could allow patients to be discharged from the hospital while awaiting a suitable donor heart might address a significant unmet need for this small patient population.

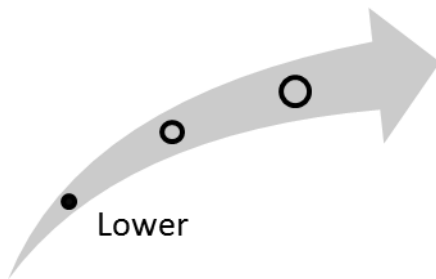
The Freedom<sup>®</sup> Driver System, also developed by SynCardia Systems, is under development to address this need. It is a wearable pneumatic driver that powers the SynCardia TAH-t. The driver is intended to allow patients receiving the TAH-t to leave the hospital and live at home while awaiting a donor heart. The patient carries the 13.5 lb pneumatic driver in a backpack or shoulder bag. The driver is powered by two onboard batteries that can be recharged with an automobile adapter or a standard electrical outlet. As with conventional, large, hospital-based pneumatic driver systems, the Freedom driver is connected to the implantable TAH-t by a flexible pneumatic driveline that passes through the patient’s skin in the left chest just below the ribs. The driver flashes a light or sounds an alarm when the system requires the user’s attention.<sup>89</sup>

In March 2010, SynCardia received CE mark approval to market the Freedom driver in the European Union for use with the SynCardia TAH-t.<sup>90</sup> The portable driver is being studied under an FDA-approved investigational device exemption (IDE) trial.<sup>89</sup> As of April 2012, the company reported, 43 patients had received the TAH-t in the clinical trial, and 30 of these patients had been discharged from the hospital using the portable driver, which is the minimum number of discharges required by the clinical trial.<sup>89</sup> Although literature search results have not identified any completed clinical trials using the driver, the clinical experiences of individual patients have been published as press releases on the manufacturer’s Web site and in one case summary.<sup>89,91</sup> The most recent (August 2012) press release on the topic stated that an adult male who received the TAH-t as a bridge to transplant logged more than 400 miles of hiking after he was discharged from the hospital on March 21, 2012, using the portable driver system.<sup>92</sup>

## **Clinical Pathway at Point of This Intervention**

ACC/AHA clinical guidelines identify cardiac transplantation or the implantation of a ventricular assist device (VAD) as the only established surgical treatments for advanced, end-stage HF.<sup>93</sup> The portable driver system is intended to complement TAH-t use.<sup>89</sup> As a bridge to transplantation, the TAH-t with the Freedom driver would complement heart transplantation. Some left VADs that are compatible with portable driver systems for in-home use could compete with the TAH-t and Freedom driver as a bridge to transplantation.

**Figure 5. Overall high-impact potential: Portable Freedom Driver for in-home support of the Total Artificial Heart**



Although the patient population for which this device is intended is small, and in-hospital driver systems already exist, a portable driver for the TAH-t system has the ability to dramatically improve patient quality of life and dramatically shift the care setting by allowing patients to return home while awaiting transplant, experts commenting on this intervention agreed. Experts also thought that this device has the potential to reduce costs associated with lengthy hospital stays and that using the portable device would require additional resources, such as training for staff and family members. Based on this input, our overall assessment is that this intervention is in the lower end of the high-potential-impact range.

## Results and Discussion of Comments

Seven experts, with clinical, research, and health systems backgrounds, offered perspectives on this intervention.<sup>94-100</sup>

Although the patient population for which this device is intended is small, experts generally agreed that an important unmet need exists for a driver system that would allow these patients to be discharged home while awaiting a heart transplant. Rather than closing a true gap in unmet need for health technology (because inpatient drivers are already available in the hospital setting), this device's greatest benefit is improving patient quality of life and affecting costs of care by shifting from inpatient to at-home care while awaiting a heart transplant.

Generally, experts were confident that this device would improve patient quality of life because of the psychological benefit of being able to remain home with family while awaiting a heart transplant and because of the potential health benefit that would arise from increased mobility. Some experts likened this technology's potential to that of ventilators and VADs, which were previously only offered in the hospital setting but have since been moved to the home care realm with positive results. Experts also suggested that a health benefit may be realized in removing patients from the hospital setting, given the high risk of nosocomial infections associated with inpatient care.

Experts noted that shifting the patient's care setting from an inpatient setting to the home is important and would likely result in a marked decrease in costs, given the expense of continual, long-term inpatient care. For this reason and for the potential improvements in quality of life and health status for patients, experts thought that both clinicians and patients would readily adopt this technology, provided long-term data are positive. Several experts also noted that extensive training (on the part of both hospital staff and patient home caregivers) would be required for diffusion of this product, but they did not think this would be a barrier to uptake. Additionally, experts thought that this shift would "substantially impact the aftercare community and require additional collaboration and coordination between inpatient and outpatient facilities."<sup>97</sup>

## **Hypertension Intervention**

## **Catheter-Based Radiofrequency Ablation (Symplicity System) Renal Denervation for Treatment-Resistant Hypertension**

Many pharmacotherapies are available for treating hypertension; however, uncontrolled hypertension persists in many patients.<sup>101</sup> Because uncontrolled hypertension is associated with high morbidity (e.g., end-stage organ damage) and mortality, novel interventions for treating this condition are needed.<sup>101</sup> The renal denervation device described in this report might offer a therapeutic intervention for patients whose hypertension remains uncontrolled despite pharmacotherapy. This device also has the potential to shift hypertension care from the realm of pharmacotherapy alone to the realm of minimally invasive, permanent procedures.

The sympathetic nervous system contributes to increases in blood pressure. In many patients with essential hypertension, efferent sympathetic outflow from the central nervous system to the kidneys is overactive. This activity modulates levels of renin release, tubular sodium reabsorption, and renal blood flow in ways that perpetuate hypertension.<sup>102</sup> Afferent renal sensory nerves, which carry signals from the kidneys to the central nervous system, also play a role in promoting sympathetic outflow and are considered additional contributors to hypertension.<sup>102</sup> Surgical disruption of renal sympathetic nerves has been explored for decades as a potentially therapeutic intervention for hypertension. However, earlier approaches usually involved radical sympathetic denervation, which reduced blood pressure but was not targeted enough to avoid perioperative and long-term complications (e.g., bowel, bladder, erectile dysfunction; postural hypotension).<sup>103</sup>

To mimic the blood pressure improvements seen with radical sympathetic denervation but avoid its associated side effects, manufacturers have begun investigating minimally invasive, catheter-based approaches to renal denervation.<sup>103</sup> One such system, the Symplicity<sup>®</sup> Renal Denervation System<sup>™</sup> (Ardian, Inc., now part of Medtronic), uses radiofrequency energy delivered via catheter technology to selectively ablate afferent and efferent renal nerves located in the adventitia of the renal arteries.<sup>102</sup> The manufacturer purports that a sustainable decrease in blood pressures is obtained by reducing the sympathetic nerve drive through bilaterally denervating the renal nerves with the Symplicity renal denervation system.<sup>104</sup> According to the manufacturer, the system comprises two components: a generator, which automatically controls the radiofrequency energy delivery and is activated by a hands-free switch; and a catheter, which applies the radiofrequency energy in the renal artery and is compatible with 6 Fr diameter guide catheters.<sup>105-107</sup>

The denervation procedure, which is conducted in a catheterization laboratory, is performed with the patient under conscious sedation and takes about 40 minutes.<sup>105,108,109</sup> The manufacturer states that the procedure involves a surgeon introducing the catheter through the femoral artery, via a guide catheter, and threading it to the renal artery. The catheter's tip is placed against the arterial wall, and clinicians deliver radiofrequency energy to the surrounding sympathetic nerves; the energy is managed via a computer-controlled algorithm.<sup>105</sup> The surgeon may apply up to six ablations, lasting up to 2 minutes each, within each renal artery.<sup>109</sup> The manufacturer states that because the one-time procedure does not involve a permanent implant, patients recover and return to daily living quickly.<sup>104</sup>

Results from a published clinical trial of the intervention in 153 patients at 19 centers in Australia, Europe, and the United States, state: "The median time from first to last radiofrequency energy ablation was 38 minutes. The procedure was without complication in 97% of patients (149 of 153). The 4 acute procedural complications included 3 groin pseudoaneurysms and 1 renal artery dissection, all managed without further sequelae. Postprocedure office BPs [blood pressures] were reduced by 20/10, 24/11, 25/11, 23/11, 26/14, and 32/14 mm Hg at 1, 3, 6, 12, 18, and 24 months,

respectively.”<sup>110</sup> Sustained blood pressure reductions were seen in a 3-year followup of patients in this study, with a mean blood pressure decrease of 31/16 mm Hg.<sup>111</sup>

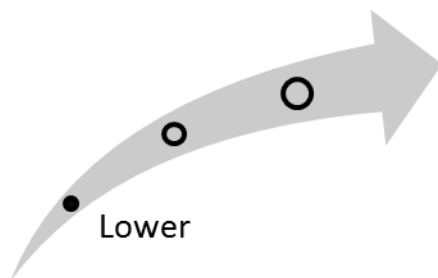
The system is approved for marketing in the European Union and Australia.<sup>112</sup> In the United States, the SYMPPLICITY HTN-3, phase III randomized controlled trial is ongoing and is expected to be completed in March 2013.<sup>113,114</sup> The trial is scheduled to enroll about 530 patients at 60 U.S. sites. The primary endpoints will be change from baseline systolic blood pressure to 6-month followup systolic blood pressure and incidence of major adverse events within 1 month after random assignment to type of treatment.<sup>113</sup>

Because Symplicity is available only for investigational use in the United States, no information is available regarding cost or insurance coverage. However, a 2012 health economics study reported that catheter-based renal denervation is a cost-effective therapeutic strategy that may lower cardiovascular morbidity and mortality in treatment-resistant hypertension.<sup>115</sup>

## Clinical Pathway at Point of This Intervention

According to the most recent report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure, lifestyle modifications (e.g., weight and diet management) are the initial interventions used in patients with hypertension. If lifestyle changes do not result in satisfactorily controlled blood pressure, pharmacotherapy is indicated.<sup>116</sup> Medical management of hypertension includes thiazide-type diuretics, used alone or in combination with one of several classes of antihypertensive agents (e.g., angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, beta blockers, or calcium channel blockers).<sup>116</sup> If the Symplicity Renal Denervation System is approved for use in the United States, it is likely to be positioned for use in patients whose hypertension is not adequately controlled with three or more antihypertensive medications and is likely to be used in conjunction with these background therapies.<sup>105,113</sup>

**Figure 6. Overall high-impact potential: catheter-based radiofrequency ablation (Symplicity System) renal denervation for treatment-resistant hypertension**



Experts commenting on this intervention agreed that it has the potential to fill an important gap in treating hypertension and would likely be somewhat accepted by clinicians and patients. However, this intervention’s potential impact is tempered by its lack of longer-term outcomes data and the likelihood that it would be easily incorporated into the existing health care infrastructure. Based on this input, our overall assessment is that this intervention is in the lower end of the high-potential-impact range.

## Results and Discussion of Comments

Seven experts, with clinical, research, health systems, and health administration backgrounds, offered perspectives on this intervention.<sup>117-123</sup>

Experts agreed that the need for interventions for treatment-resistant hypertension is important because of the size of the affected population, the morbidity and mortality associated with the

condition, and the dearth of available treatments once pharmacotherapy fails to achieve desired outcomes. Although several experts noted that the data available for the intervention are limited, experts were cautiously optimistic that this intervention is likely to improve patient health, citing the promising efficacy data that have been collected to date. However, several experts noted that longer-term studies are needed to determine whether the reduction in blood pressure that has been observed in trials translates to improved clinical outcomes and to further clarify the safety profile of the intervention.

Most experts suggested that this intervention would not especially disrupt health care infrastructure because the procedure will take place in a catheterization lab, which as one clinical expert stated, “could accommodate patient volume, assuming it is an outpatient procedure, is not associated with significant complication, and requires a single sitting application.”<sup>117</sup> However, several experts agreed that this intervention would be likely to increase the volume of patients seeking services from catheter facilities and may represent a shift in patient management over the long term should this intervention be proven to reduce the need for ongoing hypertension pharmacotherapy.

Experts were divided on whether this intervention would be readily accepted by both clinicians and patients. According to some experts, clinicians would be likely to adopt the technology because alternative treatments do not exist for this population and because the intervention requires only a one-time procedure. However, several experts thought that before adoption can occur, clinicians and patients will want to see more comprehensive safety and long-term efficacy data. Some experts suggested that the invasiveness of the procedure would pose a barrier to uptake. Most experts expected this intervention would have a moderate effect on health care costs. Although the initial procedure will be associated with an initial upfront cost, some of this initial outlay could be offset by the potential for future savings, if the intervention is proven to improve patient health.

## **Valve and Structural Disorder Interventions**



## **Percutaneous Annuloplasty (Carillon Mitral Contour System) for Treatment of Functional Mitral Regurgitation**

For patients with pharmacotherapy-refractory functional mitral regurgitation (FMR), surgical intervention is typically indicated.<sup>124</sup> However, current surgical techniques (e.g., valve repair, replacement) are associated with risk of morbidity and mortality, and many patients are ineligible for surgical intervention.<sup>124,125</sup> If approved for marketing, this percutaneous annuloplasty intervention could offer the first minimally invasive intervention for this patient population.<sup>125</sup>

Annuloplasty is a surgical procedure in which a surgeon implants a ring in the mitral valve's annulus (a fibrous tissue ring around the mitral valve opening that supports the valve leaflets) to decrease the circumference of the mitral orifice.<sup>126</sup> Percutaneous annuloplasty is a minimally invasive approach to performing the annuloplasty procedure. Surgeons use percutaneous annuloplasty to implant the device using catheters guided through the vasculature to the heart. The ring is delivered to the mitral valve through either an indirect route through the coronary sinus or a direct route through the aorta.<sup>126</sup>

The Carillon<sup>®</sup> Mitral Contour System<sup>®</sup> (Cardiac Dimensions, Inc., Kirkland, WA) is an implantable device with a percutaneous catheter delivery system. The implantable device consists of two anchors connected by a shaping ribbon. The implant is delivered using a catheter to the coronary sinus and great cardiac vein of the heart, and is designed, on deployment, to plicate the portion of the mitral annulus that the great cardiac vein surrounds. The implant is intended to diminish the mitral orifice to lessen the degree of mitral regurgitation (MR).<sup>127</sup> According to the device manufacturer, the implantation procedure is "simple" and often completed in less than an hour.<sup>127</sup>

No ongoing clinical trials investigating this device were registered with the National Clinical Trials database in the United States as of November 2012. The manufacturer reports that a European multicenter trial (TITAN II) is ongoing to investigate the safety of the device in patients with dilated ischemic or nonischemic cardiomyopathy and moderate to severe FMR.<sup>128</sup>

In a trial of the Carillon device for which results were reported in 2009, investigators enrolled 48 patients, 30 of whom received the device.<sup>129</sup> Eighteen patients did not receive the device because of access issues, insufficient acute FMR reduction, or coronary artery compromise. The major adverse event rate at 30 days was 13%; at 6 months, the degree of FMR reduction among five different quantitative echocardiographic measures ranged from 22% to 32%. Six-minute walk distance improved from a mean of 87 meters at baseline to 137 meters at 6 months after treatment ( $p < 0.001$ ). Quality of life, measured by the Kansas City Cardiomyopathy Questionnaire, improved by more than 20 points from baseline to 6 months ( $p < 0.001$ ).<sup>129</sup>

Results of the TITAN trial published in 2012 reported that using the implant produced significant clinical improvements that persisted up to 24 months in patients with FMR.<sup>130</sup> The authors reported both safety and functional data from 36 patients who permanently received the device. Fifty-three patients received the device, but 17 had to have the device recaptured. Of the 36 patients in whom the device was permanently implanted, the authors reported, "The 30-day major adverse event rate was 1.9%. In contrast to the comparison group, the implanted cohort demonstrated significant reductions in FMR as represented by regurgitant volume [baseline  $34.5 \pm 11.5$  mL to  $17.4 \pm 12.4$  mL at 12 months ( $P < 0.001$ )]. There was a corresponding reduction in LV diastolic volume [baseline  $208.5 \pm 62.0$  mL to  $178.9 \pm 48.0$  mL at 12 months ( $P = 0.015$ )] and systolic volume [baseline  $151.8 \pm 57.1$  mL to  $120.7 \pm 43.2$  mL at 12 months ( $P = 0.015$ )], compared with progressive LV [left ventricular] dilation in the comparator. The 6MWD [6-minute walk

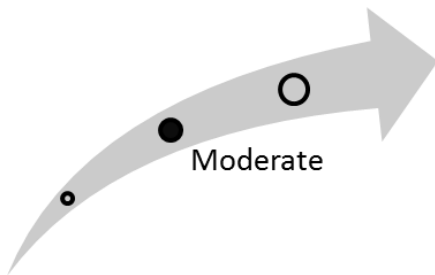
distance] markedly improved for the implanted patients by  $102.5 \pm 164$  m at 12 months ( $P = 0.014$ ) and  $131.9 \pm 80$  m at 24 months ( $P < 0.001$ ).<sup>130</sup>

This device is not yet approved for marketing in the United States, where it is limited to investigational use only.<sup>131</sup> In September 2011, the Carillon Mitral Contour System received the CE mark in Europe to treat FMR,<sup>132</sup> and the company initiated European commercialization in September 2012.<sup>133</sup>

## Clinical Pathway at Point of This Intervention

Although organic mitral valve regurgitation treatment is explicitly outlined by ACC/AHA guidelines, the optimal strategy for treating FMR is still debated.<sup>124,134</sup> This controversy stems from a growing consensus that FMR arises from ventricular etiology, not from the valve itself, prompting questions about whether treatment should target valve or ventricular pathology. For all patients with FMR, optimal medical management, including pharmacotherapies such as angiotensin-converting enzyme inhibitors, beta blockers, digitalis, diuretics, and vasodilators, is indicated. For patients whose signs and symptoms recur despite these therapies or for asymptomatic patients who have left ventricular dysfunction, surgery is indicated. Preferred surgical interventions for treating severe FMR include mitral valve replacement and mitral valve repair (e.g., annuloplasty, Alfieri correction).<sup>124</sup>

**Figure 7. Overall high-impact potential: percutaneous annuloplasty (Carillon Mitral Contour System) for treatment of functional mitral regurgitation**



Experts commenting on this intervention generally agreed that the unmet need for a less invasive alternative to surgical mitral valve repair is important. However, expert uncertainty about the device's long-term safety and efficacy profiles indicates that more data are needed to determine whether this approach will fulfill its potential. Should the device be proven safe and effective, experts thought, it could reduce recovery time and hospital length-of-stay for patients, and they thought that the device would be readily adopted by clinicians and patients. Based on this input, our overall assessment is that this intervention is in the moderate high-potential-impact range.

## Results and Discussion of Comments

Six experts, with clinical, research, and health systems backgrounds, offered perspectives on this intervention.<sup>135-140</sup> Most of the experts agreed that the unmet need for a less invasive alternative to surgical mitral repair is important and that the Carillon system may offer a treatment option for patients who are ineligible for surgery. However, some experts opined that because surgical mitral repair is already available, the unmet need that this intervention purports to address is somewhat incremental.

In terms of improving health outcomes, some experts suggested that this intervention might improve patient health by sparing them the morbidity and mortality that they would incur if they were to undergo surgical intervention. However, experts who formed their opinion of the device's

efficacy based on trial data were less optimistic, stating that although the data are somewhat promising, more data are needed to clarify the device's long-term efficacy and safety profiles. Experts also commented that for this procedure to diffuse, data comparing it to alternative therapeutic options (e.g., medical management, surgical intervention) would be necessary.

Experts thought that should this device become diffused, it has the potential to effect moderate changes to current health system operations, including shortening hospital stays and recovery times for patients. Although some experts suggested that this intervention would require less technical experience to perform than surgical mitral valve repair, other experts disagreed, stating that this intervention is likely to require significant clinician training.

In general, experts thought that this intervention would be adopted by both clinicians and patients because of the “less invasive nature of the procedure, probably lower complication rate, and relatively simplicity of the procedure compared to open surgical mitral valve repair,” along with the “probably shorter hospital stay and probably shorter recovery time.”<sup>137</sup> However, some experts suggested that this intervention may cause competition between interventionists and cardiac surgeons as to who will treat patients.

## Transcatheter Aortic Valve Implantation (CoreValve; Sapien) for Treatment of Severe Aortic Stenosis

The gold standard for treating aortic stenosis is open surgical replacement of the valve with a mechanical valve or a bioprosthetic valve.<sup>141-143</sup> However, open-heart surgery is typically not an option for patients at high risk of experiencing surgical complications.<sup>141,142,144</sup> Thus, manufacturers have developed minimally invasive approaches to valve replacement to extend the therapeutic benefit of aortic valve replacement to inoperable and high-risk surgical patients.<sup>142,144</sup>

Medtronic developed the CoreValve<sup>®</sup> System, which is being investigated in the United States for treating severe aortic stenosis.<sup>145</sup> The system is intended for use in patients who are not surgical candidates or who are at high surgical risk. The system features a porcine pericardial tissue valve mounted in a self-expanding, hourglass-shaped, nitinol-alloy mesh frame. The bioprosthetic valve is deployed using an 18 Fr diameter delivery catheter with a set of disposable catheter-loading components.<sup>146</sup> According to the manufacturer, the implantation procedures lasts about 1–3 hours, and patients are typically sedated. The clinician guides a sheath into the heart, then threads a balloon catheter through the sheath into the heart. Once the balloon is positioned in the aortic valve, it is inflated, preparing the aortic valve for implantation of the CoreValve. Using imaging equipment to direct placement, the clinician situates the CoreValve over the diseased aortic valve. In some cases, the diseased valve is completely removed before the CoreValve is placed. The manufacturer claims that the CoreValve begins working immediately. The catheter is removed, and the incision is closed. The manufacturer states that the typical hospital stay following a transcatheter aortic valve implantation (TAVI; also known as transcatheter aortic valve replacement [TAVR]) procedure is 3–5 days.<sup>147</sup>

In May 2007, CoreValve received CE mark for the CoreValve Percutaneous ReValving<sup>™</sup> System for treating high-risk patients.<sup>148</sup> In September 2010, Medtronic received the CE mark for the CoreValve delivery system with AccuTrak<sup>™</sup> stability layer for TAVI.<sup>149</sup> Medtronic received a CE mark in September 2012 for the newest valve addition to the system, the CoreValve Evolut, a 23 mm valve that can fit an aortic annulus size of 18 mm. The CoreValve System now has four valve sizes ( 23, 26, 29, and 31 mm) to fit aortic annulus sizes that range from 18 mm to 29 mm.<sup>148</sup> Medtronic received an IDE for its CoreValve trial from FDA in October 2010<sup>150</sup> and is recruiting patients for a phase III multicenter TAVI trial for patients with severe aortic stenosis who are at very high risk of complications if they undergo surgery. Medtronic estimates an enrollment of 2,250 participants and a completion date of January 2019.<sup>151</sup> Medtronic is also conducting a clinical trial (SURTAVI) to investigate the CoreValve System's safety and efficacy in patients with severe aortic stenosis who have an intermediate risk of surgical complications. This clinical trial will compare TAVI using the CoreValve System with surgical aortic valve replacement. The company estimates an enrollment of 2,500 participants for this study.<sup>152</sup>

In an October 2012 press release, Medtronic announced that initial 1-year results from its international postmarket clinical trial (ADVANCE) show high 1-year survival rates (82.1% survival, 88.2% cardiovascular survival) and statistically significant 1- and 6-month improvements in quality of life for patients receiving the CoreValve System.<sup>153,154</sup>

Edwards Lifesciences Corp. (Irvine, CA) developed the Sapien<sup>™</sup> Transcatheter Heart Valve for use in patients with severe aortic stenosis who are at high surgical risk or who are not surgical candidates.<sup>144</sup> The bioprosthesis features a bovine pericardial tissue aortic valve affixed within a balloon-expandable stainless-steel frame.<sup>155</sup> The valves are available in 23 and 26 mm sizes to accommodate different aortic annulus sizes.<sup>155</sup> The RetroFlex<sup>®</sup> and RetroFlex II<sup>™</sup> delivery catheters

are used to deploy the valve using femoral artery access, and the Ascendra™ delivery system is designed to implant the valve via minimally invasive surgery using a transapical approach.<sup>156,157</sup>

According to an informational guide published by the manufacturer, for Sapien TAVI by the transfemoral approach, the patient is placed under general anesthesia and an incision is made in the patient's groin, where the physician places a sheath in the femoral artery. A balloon catheter is used to stretch the aortic valve opening. A member of the operating team places the valve on the delivery system and crimps it to allow insertion into the body through the sheath. Using fluoroscopic guidance, the surgeon inserts the valve and delivery system through the sheath and guides it to the aortic valve. Once the new valve is positioned, the balloon is filled with liquid, expanding the new valve from its crimped mode to its functional mode. The implant is checked for proper function, the delivery system is removed, and the incision is closed. The manufacturer states that the valve begins working immediately. The procedure takes up to 4 hours, and the average hospital stay for a patient undergoing TAVI is 2–6 days.<sup>158</sup>

In an April 2011 press release, Edwards Lifesciences reported results of the PARTNER trial, which were included in the FDA premarket approval submission:

In patients with aortic stenosis at high risk for surgery, transcatheter aortic valve replacement (TAVR) was non-inferior to surgical aortic valve replacement (AVR) for all-cause mortality at one year, 24.2 percent versus 26.8 percent, respectively. In addition, mortality at 30 days was lower than expected in both arms of the trial, with TAVR at 3.4 percent and AVR at 6.5 percent. The observed mortality in these AVR patients was lower than the thought risk of operative mortality of 11.8 ... . Both TAVR and AVR were associated with important but different peri-procedural hazards. The study demonstrated that major vascular complications and neurological events were more frequent with TAVR, while major bleeding and new onset atrial fibrillation were more frequent with AVR. Symptom improvement as measured by the New York Heart Association (NYHA) class and six-minute walk distance favored TAVR at 30 days and was similar to AVR at one year.<sup>159</sup>

In November 2011, FDA approved the Sapien for transfemoral delivery in patients who have severe, symptomatic aortic stenosis and who have been determined by a cardiac surgeon to be inoperable for open aortic valve replacement and in whom existing comorbidities would not preclude the expected benefit from the procedure.<sup>160</sup> The company also stated the following conditions of approval: “As part of this approval, FDA has requested the implementation of two substantial post-approval studies. One study will follow patients already enrolled in The PARTNER Trial, and the second study will track new U.S. patients. The company anticipates the second study will be incorporated into a new national patient registry.”<sup>160</sup> In October 2012, FDA expanded the Sapien labeling to include patients with severe aortic stenosis who are high risk of experiencing complications from open-heart valve surgery. This approval was for both transfemoral and transapical delivery of the Sapien valve in this patient population.<sup>161,162</sup>

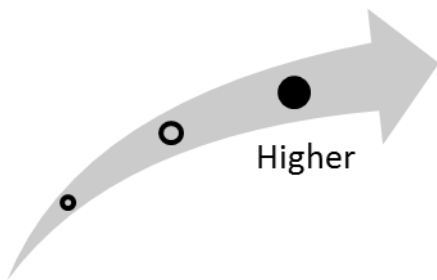
In 2011, Reynolds reported a cost-effectiveness comparison between TAVI and open-heart aortic valve replacement among Cohort A (high-risk) patients in the PARTNER trial. The authors reported that for transfemoral TAVI, procedural costs were substantially higher than those for open-heart aortic valve replacement (\$34,863 vs. \$14,451). However, overall treatment costs for the entire index hospitalization were somewhat lower for transfemoral TAVI than for open surgery (\$71,955 vs. \$74,452,  $p=0.53$ ). The \$2,497 cost reduction in favor of transfemoral TAVI was because of lower nonprocedural costs (\$31,192 vs. \$54,228), mainly a 6.2-day shorter length of stay in the transfemoral TAVI group (10.2 vs. 16.4 days,  $p<0.001$ ).<sup>163</sup>

In May 2012, CMS released a national coverage determination for TAVI, stating that CMS “covers transcatheter aortic valve replacement (TAVR) under Coverage with Evidence Development (CED)” when it the procedure is used for “the treatment of symptomatic aortic valve stenosis when furnished according to an FDA approved indication” and when certain conditions are met.<sup>164</sup> The coverage determination detailed criteria for the required infrastructure, interdisciplinary team members, number of procedures to achieve and maintain proficiency, and other requirements.

## Clinical Pathway at Point of This Intervention

According to 2006 guidelines by ACC/AHA, aortic valve replacement is considered the surgical treatment of choice for most adults with severe aortic stenosis who are candidates for open heart surgery.<sup>134</sup> However, some patients are not candidates for surgical aortic valve replacement and therefore have a poor prognosis. Previously, patients who were not candidates for aortic valve replacement surgery could have their symptoms managed through aortic balloon valvuloplasty or medical management with pharmacologic agents. However, these options do not provide full relief of aortic stenosis symptoms; the only definitive treatment is aortic valve replacement.<sup>141,142,165</sup> The advent of TAVI provides a new option for patients with severe aortic stenosis who are not candidates for surgery or who are at high risk of complications if they undergo surgery. Many of these patients would have no treatment options otherwise.<sup>144,151,152,162</sup>

**Figure 8. Overall high-impact potential: transcatheter aortic valve implantation (CoreValve; Sapien) for treatment of severe aortic stenosis**



Experts commenting on this intervention agreed that it would offer an important new treatment modality for patients who have no other medical or surgical treatment option. Experts thought that this intervention would improve patient health outcomes, and they thought an increase in patient volume and a shift in care setting (from outpatient to inpatient) would be seen as this intervention diffuses. Experts experienced in the procedure pointed out that establishing a program puts a significant strain on conventional resources and requires additional infrastructure to evaluate potential patients. Others were less familiar with how disruptive the intervention would be to health care infrastructure but agreed that the intervention has the potential to both increase (in the short term) and decrease (in the long term) health care costs. Based on this input, our overall assessment is that this intervention is in the higher end of the high-potential-impact range.

## Results and Discussion of Comments

Seven experts, with clinical, research, and health system backgrounds, offered perspectives on the CoreValve technology.<sup>166-172</sup> Six experts, with similar backgrounds, offered perspectives on the Sapien technology.<sup>173-178</sup> Two of these experts claimed potential conflicts of interest because they both are involved in implanting these valves in their respective medical centers. These potential conflicts of interest are balanced by experts who did not claim conflicts of interests.<sup>173,178</sup>

Expert opinions concurred that the unmet need addressed by this intervention is extremely important, in light of the large number of patients who would be affected and the fact that no other therapies are available for this population. As one clinical expert stated: “There is a large gap for certain patient populations. Patients currently deemed too high a risk for surgery have only a medical option [and] medical therapy has no impact on the natural history of the disease, thus mortality is high.”<sup>178</sup> Furthermore, experts asserted that this patient population is growing as the U.S. population ages and as better techniques for identifying patients with aortic stenosis are developed.

Experts were optimistic about this intervention’s ability to meet the unmet need and improve patient health outcomes, mostly due to encouraging data from clinical trials, but also because no other options are available for this population. Some experts suggested that over time, this intervention may be extended to patients who are “less ill,” as well, although data on safety and durability of the procedure for this expanded patient population are needed.

Experts had differing opinions about the extent to which this technology would disrupt current health care infrastructure and patient management models. Some experts stated that this intervention could be conducted in existing facilities, thereby not markedly disrupting current infrastructure, but one clinical expert with experience in the technology stated, “Starting a TAVR program ... is a huge undertaking. It is not just adding another procedure, it is adding a whole new program to a medical center. The resource utilization is considerable. The program will put a significant strain on conventional resources and require an additional infrastructure to evaluate potential patients.”<sup>170</sup> One notable consequence of this intervention is the shift in care setting for patients who typically would have been treated only with medical therapy. Patient volume is expected to rise accordingly, and even if patients referred for evaluation are not candidates for TAVI, the referrals alone are expected to increase patient volumes.

Experts thought that clinicians who would perform this procedure would readily accept this technology, considering that no other interventions are available for this patient population, but actual adoption may be slow, given that the procedure is likely to be rolled out only in selected centers at first. Experts also generally thought that patients would accept this procedure because it offers a therapeutic option where previously none existed and because the intervention is considered minimally invasive.

Experts were confident that this intervention would have a significant impact on health care costs for payers and hospitals. Cost of care for patients previously treated with medical therapy who are eligible for and undergo TAVI will increase. The device itself is costly (\$32,500), and the deployment procedure is costly, even though the hospital stay might be shorter than open surgery. Also, Medicare reimbursement rates may not cover costs of the device and procedure, so hospitals might lose revenue on the procedure, although that might be offset by an increase in referrals that end up receiving other non-TAVI treatment (such as open surgery). Several experts noted that some costs associated with medically managing patients with end-stage disease might decrease (e.g., hospitalizations) after patients undergo TAVI because they would not be expected to need pharmaceutical treatment and because hospitalizations for complications in patients previously on medical therapy could decrease.

## Transcatheter Mitral Valve Repair (MitraClip) for Treatment of Mitral Regurgitation

Although open surgical repair of the mitral valve is considered the gold standard treatment for MR, some patients are not candidates for surgery because of their high risk of complications.<sup>179,180</sup> Thus, an unmet need exists for an intervention that offers a less invasive alternative to open surgical mitral valve repair.

The MitraClip device (Abbott Laboratories, Abbott Park, IL) is intended to simulate the functional effects achieved by the Alfieri edge-to-edge surgical procedure, an open surgery repair technique used for treating MR.<sup>180</sup> In the Alfieri procedure, a surgeon sutures together the edges of the two opposing mitral valve leaflets at the center of the valve opening, leaving two smaller openings on either side that close more completely than a single large opening.<sup>181</sup> The MitraClip device mimics this procedure by “clipping together” the mitral valve leaflets, rather than using sutures.<sup>180,182</sup>

The MitraClip is an implantable, two-armed, flexible, metal clip made of cobalt and chromium and covered in polyester fabric. It is intended to help the mitral valve close more completely, thereby potentially reducing MR.<sup>183</sup> The MitraClip system consists of the clip device, a clip-delivery system, and a steerable guide catheter. To implant the device, the patient is placed under general anesthesia (but no heart-lung machine is required), and the clinician inserts the guide catheter through the femoral vein into the heart and, using the catheter and the clip-delivery systems, delivers and deploys the clip device.<sup>184</sup> The device is placed by advancing the guide catheter into the left atrium and positioning the opened clip over the mitral valve. The surgeon advances the clip to the left ventricle and closes its arms, clamping the mitral valve leaflets together. At this point, MR is assessed; if the change in MR is not satisfactory, the clip is repositioned. The implantation procedure requires a trans-septal puncture, which has been called a “crucial early step” in the procedure. The procedure is performed in a catheterization laboratory using fluoroscopic and echocardiographic guidance.<sup>180</sup> The manufacturer states that recovery typically lasts 1–3 days.<sup>184</sup>

The MitraClip is not yet FDA approved for marketing. Originally, the company expected FDA to review its premarket approval submission in 2011; however, in May 2011, the manufacturer issued a voluntary recall of the device in Europe, Australia, Singapore, and other countries where the device had been approved because of issues with the delivery catheter’s tip. Although the company resolved the issue and reintroduced the device in those countries, the recall prompted FDA to request additional information and analysis regarding the MitraClip, which the company provided.<sup>185</sup> The MitraClip is under evaluation in a phase III clinical trial (EVEREST II) in the United States, with estimated completion by December 2017.<sup>186</sup>

In 2012, investigators from a clinical trial of 78 patients with significant MR in whom the device was implanted, reported the following:<sup>179</sup>

Seventy-eight patients underwent the MitraClip procedure. Their mean age was 77 years, >50% had previous cardiac surgery, and 46 had functional MR and 32 degenerative MR. MitraClip devices were successfully placed in 96% of patients. Protocol-predicted surgical mortality rate in the HRS [high risk study] and concurrent comparator group was 18.2% and 17.4%, respectively, and Society of Thoracic Surgeons calculator estimated mortality rate was 14.2% and 14.9%, respectively. The 30-day procedure-related mortality rate was 7.7% in the HRS and 8.3% in the comparator group ( $p = \text{NS}$ ). The 12-month survival rate was 76% in the HRS and 55% in the concurrent comparator group ( $p = 0.047$ ). In surviving patients with matched baseline and 12-month data, 78%



had an MR grade of  $\leq 2+$ . [LV] end-diastolic volume improved from 172 ml to 140 ml and end-systolic volume improved from 82 ml to 73 ml (both  $p = 0.001$ ). [NYHA] functional class improved from III/IV at baseline in 89% to class I/II in 74% ( $p < 0.0001$ ). Quality of life was improved ([SF-36] physical component score increased from 32.1 to 36.1 [ $p = 0.014$ ] and the mental component score from 45.5 to 48.7 [ $p = 0.065$ ]) at 12 months. The annual rate of hospitalization for congestive heart failure in surviving patients with matched data decreased from 0.59 to 0.32 ( $p = 0.034$ )."

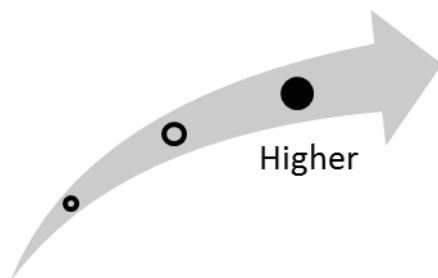
Additionally, in study results reported in 2012, investigators reported that 3-year data from the EVEREST II trial confirmed the improved safety and clinical benefits of the MitraClip compared with surgically treating severe MR at 3-year followup. This study found a freedom-from-mortality rate of 87% for patients treated with the MitraClip compared with 85% for surgery patients, and a freedom-from-surgery rate of 78% for MitraClip patients compared with a freedom-from-resurgery rate of 96% for surgery patients.<sup>187</sup>

Cost information for the device or procedure in the U.S. market is not yet available; however, a cost-effectiveness study found that the percutaneous clip technology for MR is equal or less in cost when compared with the cost of standard surgical therapy.<sup>188</sup>

## Clinical Pathway at Point of This Intervention

The preferred treatment for severe MR is surgical valve repair or replacement.<sup>179,180</sup> ACC/AHA clinical guidelines recommend surgical mitral repair over mitral valve replacement in most patients because the "valve is suitable for repair and appropriate surgical skill and expertise are available."<sup>134</sup> If approved for marketing in the United States, the MitraClip would be positioned as a percutaneous alternative to surgical valve repair.<sup>179,180</sup>

**Figure 9. Overall high-impact potential: transcatheter mitral valve repair (MitraClip) for treatment of mitral regurgitation**



Overall, experts agreed this procedure addresses a considerable unmet need and has the potential to improve patient health, although some experts agreed that more data concerning safety and long-term outcomes are needed. Experts had differing opinions about how much this intervention would disrupt current health care delivery for this condition. Some experts believed the disruption to health care delivery would be limited because the infrastructure is already in place, although other experts believe that the increase in patient volume has potential to cause a large disruption to health care delivery. The majority of experts believe the MitraClip would increase health care costs but thought that more long-term data were needed to determine whether it would reduce costs of therapy for this population over the long term.

## Results and Discussion of Comments

Eight experts, with clinical, research, health systems, and health administration backgrounds, offered perspectives on this technology.<sup>189-196</sup> The majority of experts agreed that the unmet need for less invasive interventions to treat MR is important because of the large number of patients with MR who are not candidates for surgical repair. Two experts thought this device has relatively low overall potential to fulfill the unmet need, with one stating that this is just another treatment option for patients with MR.<sup>190</sup> Another expert believes that the procedure is highly risky and that more data demonstrating safe and reliable outcomes would be needed for it to have a greater potential in fulfilling the unmet need. Although these two experts thought the device has limited potential, the other experts thought that this device has promise for fulfilling the unmet need, especially for patients at high surgical risk. One expert also noted that patients with secondary MR and significant LV dysfunction would be good candidates for this procedure.<sup>189</sup>

Most experts believe the device has potential to improve health outcomes, although several stated that more clinical data would be beneficial in determining both the long-term benefits and true therapeutic potential. One expert believes that the MitraClip has great potential to improve health outcomes in both patients with primary mitral disease with MR that originates from the center of the valve and patients with relatively normal valve tissue who have secondary MR due to chamber enlargement or dysfunction.<sup>189</sup> This expert also thought MitraClip might serve as an intermediate treatment for patients with severe dilated cardiomyopathy. Some experts expressed concerns about the safety and believe that the numerous comorbidities seen in these patients would present risk and preclude some patients from achieving greatly improved outcomes. Experts all agreed that this device would have little effect on health care disparities.

Because the MitraClip is intended for patients who are at risk of complications from surgery, some experts believe that this device would have a large potential to disrupt the health care delivery system because of the increased volume of patients coming to the hospital for the procedure. Other experts believe that the infrastructure to carry out this procedure is already in place in most interventional facilities; therefore, it should not greatly disrupt the health care delivery infrastructure, with increased patient volume being the only potential disruption. The majority of experts, however, agreed that this device would have great potential to disrupt current management of patients with MR because the MitraClip would offer an option to many patients who are medically managed currently. One expert disagreed, stating that any change in patient management would be gradual and, therefore, would not disrupt the way patients with MR are currently managed.<sup>189</sup>

Although most experts agreed that the MitraClip implant would entail a significant learning curve for clinicians, with considerable training requirements, they agreed that if clinical trial data continue to demonstrate benefits and safety, clinical acceptance of the device would be expected. All experts agreed that with sufficient data of safety and effectiveness, patients would likely accept this device as a minimally invasive therapeutic option for MR because of its potential to improve health outcomes in patients who cannot be treated surgically. Two experts suggested that cost may also influence patient acceptance, with one believing it could have a positive impact because of decreased treatment costs<sup>190</sup> and the other believing acceptance would be limited if insurance does not cover the procedure.<sup>195</sup>

One expert noted that this procedure is not intended to completely repair mitral valves; therefore, patients who are eligible for surgery may opt for surgery to achieve a complete, rather than partial, repair.<sup>189</sup>

Experts generally agreed that the MitraClip device and its related procedure would be expensive and affect health care costs. The importance of long-term studies in determining overall impact on

health care costs was noted by most experts. A few experts thought that the MitraClip would have minimal impact on health care costs, reasoning that this procedure would be less costly compared with surgical treatment or long-term care of patients not eligible for surgery.

## References

1. Nordbeck P, Weiss I, Ehses P, et al. Measuring RF-induced currents inside implants: impact of device configuration on MRI safety of cardiac pacemaker leads. *Magn Reson Med* 2009 Mar;61(3):570-8. PMID: 19132759
2. Medtronic receives FDA approval for first and only pacemaker system in the U.S. designed for use in the MRI environment. [internet]. Minneapolis (MN): Medtronic, Inc.; 2011 Feb 8 [accessed 2011 Feb 11]. [4 p]. Available: <http://wwwp.medtronic.com/Newsroom/NewsReleaseDetails.do?itemId=1297193518258>.
3. Medtronic receives FDA panel's unanimous recommendation for approval of Revo MRI SureScan pacing system. [internet]. Minneapolis (MN): Medtronic, Inc.; 2010 Mar 19 [accessed 2010 Dec 31]. [4 p]. Available: <http://wwwp.medtronic.com/Newsroom/NewsReleaseDetails.do?itemId=1269036141493>.
4. Medtronic receives CE mark for second-generation MRI pacemaker. [internet]. Minneapolis (MN): Medtronic, Inc.; 2009 Jun 19 [accessed 2010 Dec 31]. [3 p]. Available: [http://wwwp.medtronic.com/Newsroom/NewsReleaseDetails.do?itemId=1245340154210&lang=en\\_US](http://wwwp.medtronic.com/Newsroom/NewsReleaseDetails.do?itemId=1245340154210&lang=en_US).
5. Wilkoff BL, Bello D, Taborsky M, et al. Magnetic resonance imaging in patients with a pacemaker system designed for the magnetic resonance environment. *Heart Rhythm* 2011 Jan;8(1):65-73. PMID: 20933098
6. Medtronic USA, Inc. price list update. [internet]. New York State Office of General Services; 2012 Oct 10 [accessed 2012 Nov 13]. [4 p]. Available: [http://www.ogs.state.ny.us/purchase/spg/pdfdocs/1260121174PL\\_MedtronicUSA.pdf](http://www.ogs.state.ny.us/purchase/spg/pdfdocs/1260121174PL_MedtronicUSA.pdf).
7. National Coverage Determination (NCD) for cardiac pacemakers (20.8). [internet]. Baltimore (MD): Centers for Medicare & Medicaid Services (CMS); 2004 [accessed 2012 Nov 13]. [4 p]. Available: <http://www.cms.gov/medicare-coverage-database/details/ncd-details.aspx?NCDId=238&ncdver=2&bc=BAABAAAAAA>.
8. Centers for Medicare and Medicaid Services (CMS). Decision memo for magnetic resonance imaging (MRI) (CAG-00399R3). Baltimore (MD): Centers for Medicare and Medicaid Services (CMS); 2011 Jul 7. 11 p. Also available: [https://www.cms.gov/medicare-coverage-database/details/nca-decision-memo.aspx?&NcaName=Magnetic%20Resonance%20Imaging%20\(MRI\)%20\(3rd%20Recon\)&bc=ACAAAAAIAAAA&NCAId=252&](https://www.cms.gov/medicare-coverage-database/details/nca-decision-memo.aspx?&NcaName=Magnetic%20Resonance%20Imaging%20(MRI)%20(3rd%20Recon)&bc=ACAAAAAIAAAA&NCAId=252&).
9. Epstein AE, DiMarco JP, Ellenbogen KA, et al. ACC/AHA/HRS 2008 guidelines for device-based therapy of cardiac rhythm abnormalities: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the ACC/AHA/NASPE 2002 Guideline Update for Implantation of Cardiac Pacemakers and Antiarrhythmia Devices) developed in collaboration with the American Association for Thoracic Surgery and Society of Thoracic Surgeons. *J Am Coll Cardiol* 2008 May 27;51(21):e1-62. PMID: 18498951
10. Hundley WG, Bluemke DA, Finn JP, et al. ACCF/ACR/AHA/NASCI/SCMR 2010 expert consensus document on cardiovascular magnetic resonance: A report of the American College of Cardiology Foundation task force on expert consensus documents. *Circulation* 2010 Jun 08;121(22):2462-508.
11. Expert Commenter 669. (External, Research/Scientific/Technical). Horizon Scanning Structured Comment Form. HS614 - Cardiac pacing system (REVO) for patients who may require future magnetic resonance imaging. 2012 Apr 18 [review date].
12. Expert Commenter 596. (External, Clinical). Horizon Scanning Structured Comment Form. HS614 - Cardiac pacing system (REVO) for patients who may require future magnetic resonance imaging. 2012 Apr 23 [review date].
13. Expert Commenter 418. (ECRI Institute, Technology Assessment). Horizon Scanning Structured Comment Form. HS614 - Cardiac pacing system (REVO) for patients who may require future magnetic resonance imaging. 2012 Apr 16 [review date].

14. Expert Commenter 394. (ECRI Institute, Applied Solutions Group). Horizon Scanning Structured Comment Form. HS614 - Cardiac pacing system (REVO) for patients who may require future magnetic resonance imaging. 2012 Apr 19 [review date].
15. Expert Commenter 614. (ECRI Institute, Health Devices). Horizon Scanning Structured Comment Form. HS614 - Cardiac pacing system (REVO) for patients who may require future magnetic resonance imaging. 2012 Apr 16 [review date].
16. Expert Commenter 546. (External, Health Systems/Administration). Horizon Scanning Structured Comment Form. HS614 - Cardiac pacing system (REVO) for patients who may require future magnetic resonance imaging. 2012 Apr 25 [review date].
17. Expert Commenter 423. (ECRI Institute, Technology Assessment). Horizon Scanning Structured Comment Form. HS614 - Cardiac pacing system (REVO) for patients who may require future magnetic resonance imaging. 2012 Apr 19 [review date].
18. Bardy GH, Smith WM, Hood MA, et al. An entirely subcutaneous implantable cardioverter-defibrillator. *N Engl J Med* 2010 Jul 1;363(1):36-44. PMID: 20463331
19. Boston Scientific receives FDA approval of first-in-class S-ICD System for patients at risk of sudden cardiac arrest. [internet]. Natick (MA): Boston Scientific Corporation; 2012 Sep 28 [accessed 2012 Oct 2]. [2 p]. Available: <http://bostonscientific.mediaroom.com/2012-09-28-Boston-Scientific-Receives-FDA-Approval-of-First-in-Class-S-ICD-System-for-Patients-at-Risk-of-Sudden-Cardiac-Arrest>.
20. Boston Scientific Corporation. Effective defibrillation without transvenous leads. [internet]. Natick (MA): Boston Scientific Corporation [accessed 2012 Nov 14]. [1 p]. Available: <http://www.bostonscientific.com/cardiac-rhythm-resources/cameron-health/sicd-components.html>.
21. Cameron Health commences FDA-approved IDE clinical trial of the minimally invasive totally subcutaneous implantable defibrillator for treatment of sudden cardiac arrest. [internet]. San Clemente (CA): Cameron Health, Inc.; 2010 Mar 18 [accessed 2011 Feb 22]. [3 p]. Available: <http://physician.cameronhealth.com/news1.htm>.
22. A new category of protection that leaves the vasculature untouched. [internet]. Natick (MA): Boston Scientific Corporation [accessed 2012 Nov 14]. [2 p]. Available: <http://www.bostonscientific.com/cardiac-rhythm-resources/cameron-health/sicd-implant.html>.
23. A patient guide: living with your S-ICD system. San Clemente (CA): Cameron Health, Inc.; 2009 Jun. What is the minimally invasive S-ICD system? p. 13-5. Also available: <http://www.cameronhealth.com/documents/NewPatientGuide.pdf>.
24. Gold MR, Theuns DA, Knight BP, et al. Head-to-head comparison of arrhythmia discrimination performance of subcutaneous and transvenous ICD arrhythmia detection algorithms: the START study. *J Cardiovasc Electrophysiol* 2012 Apr;23(4):359-66. Epub 2011 Oct 28. PMID: 22035049
25. Miller R. EFFORTLESS: registry shows continued improvement with subcutaneous ICD. In: Heartwire [internet]. New York (NY): TheHeart.org; 2012 Jun 15 [accessed 2012 Nov 20]. [3 p]. Available: <http://www.theheart.org/article/1415303.do>.
26. Reed V. Defibrillator maker Cameron drawing attention. [internet]. Orange County Business Journal; 2010 Jul 26 [accessed 2011 Feb 14]. [2 p]. Available: <http://www.ocbj.com/news/2010/jul/25/defibrillator-maker-cameron-drawing-attention/>.
27. Subcutaneous implantable cardioverter-defibrillator (ICD). [internet]. Birmingham (UK): EuroScan International Network; 2012 Nov 20 [accessed 2012 Nov 20]. [4 p]. Available: <http://euroscan.org.uk/technologies/technology/view/1704>.
28. Centers for Medicare & Medicaid Services (CMS). Decision memo for implantable cardioverter defibrillators (ICDs) (CAG-00157N). [internet]. Baltimore (MD): Centers for Medicare & Medicaid Services (CMS), Department of Health and Human Services; 2003 Jun 6 [accessed 2012 Nov 20]. [15 p]. Available: <http://www.cms.gov/medicare-coverage-database/details/nca-decision-memo.aspx?NCAId=39&fromdb=true>.

29. Excellus Health Plan, Inc. Endovascular repair (coil embolization) of intracranial aneurysms. Policy number: 7.01.81. Rochester (NY): Excellus Health Plan, Inc.; 2012 Sep 20. 8 p. Also available:  
<https://www.excellusbcbs.com/wps/wcm/connect/0ba5f7004e8eb67d8e97bfe420b83c88/mp+endo+intracran+aneur+tac+12.pdf?MOD=AJPERES>.
30. BlueCross BlueShield of North Carolina. Corporate medical policy: implantable cardioverter defibrillator. Durham (NC): BlueCross BlueShield of North Carolina; 2012 Oct. 5 p. Also available:  
[https://www.bcbsnc.com/assets/services/public/pdfs/medicalpolicy/implantable\\_cardioverter\\_defibrillator\\_notification.pdf](https://www.bcbsnc.com/assets/services/public/pdfs/medicalpolicy/implantable_cardioverter_defibrillator_notification.pdf).
31. BlueCross BlueShield of Arizona. Medical coverage guidelines: implantable cardioverter defibrillator, subcutaneous. Phoenix (AZ): BlueCross BlueShield of Arizona; 2012 Oct 31. 2 p. Also available:  
<https://secure.azblue.com/pdf/medpol/o655.pdf>.
32. European Heart Rhythm Association, Heart Rhythm Society, Zipes DP, et al. ACC/AHA/ESC 2006 guidelines for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: a report of the American College of Cardiology/American Heart Association Task Force and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Develop Guidelines for Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death. J Am Coll Cardiol 2006 Sep 5;48(5):e247-346. PMID: 16949478
33. Expert Commenter 524. (ECRI Institute, Technology Assessment). Horizon Scanning Structured Comment Form. HS168 - Subcutaneous implantable cardioverter defibrillator (S-ICD System) for treatment of cardiomyopathy. 2012 Apr 10 [review date].
34. Expert Commenter 676. (PRI, Health Systems/Administration). Horizon Scanning Structured Comment Form. HS168 - Subcutaneous implantable cardioverter defibrillator (S-ICD System) for treatment of cardiomyopathy. 2012 Mar 20 [review date].
35. Expert Commenter 769. (External, Clinical). Horizon Scanning Structured Comment Form. HS168 - Subcutaneous implantable cardioverter defibrillator (S-ICD System) for treatment of cardiomyopathy. 2012 Apr 24 [review date].
36. Expert Commenter 403. (ECRI Institute, Technology Assessment). Horizon Scanning Structured Comment Form. HS168 - Subcutaneous implantable cardioverter defibrillator (S-ICD System) for treatment of cardiomyopathy. 2012 Apr 10 [review date].
37. Expert Commenter 1157. (External, Clinical). Horizon Scanning Structured Comment Form. HS168 - Subcutaneous implantable cardioverter defibrillator (S-ICD System) for treatment of cardiomyopathy. 2012 Mar 23 [review date].
38. Expert Commenter 397. (ECRI Institute, Applied Solutions Group). Horizon Scanning Structured Comment Form. HS168 - Subcutaneous implantable cardioverter defibrillator (S-ICD System) for treatment of cardiomyopathy. 2012 Apr 10 [review date].
39. Liebeskind DS. Cerebral aneurysms. In: eMedicine [now Medscape Reference] [internet]. New York (NY): WebMD, LLC; 1994- [updated 2012 Feb 27]. [accessed 2004 Sep 28]. [2 p]. Available:  
<http://emedicine.medscape.com/article/1161518-overview>.
40. Cerebral aneurysm: patient information. [internet]. Rolling Meadows (IL): American Association of Neurological Surgeons (AANS); 2009 Aug [accessed 2012 Mar 19]. [6 p]. Available:  
<http://www.aans.org/Patient%20Information/Conditions%20and%20Treatments/Cerebral%20Aneurysm.aspx>.
41. What you should know about cerebral aneurysms. [internet]. American Heart Association; 2012 Nov 8 [accessed 2012 Nov 14]. [4 p]. Available:  
[http://www.strokeassociation.org/STROKEORG/AboutStroke/TypesofStroke/HemorrhagicBleeds/What-You-Should-Know-About-Cerebral-Aneurysms\\_UCM\\_310103\\_Article.jsp](http://www.strokeassociation.org/STROKEORG/AboutStroke/TypesofStroke/HemorrhagicBleeds/What-You-Should-Know-About-Cerebral-Aneurysms_UCM_310103_Article.jsp).
42. Understanding: brain aneurysm statistics and facts. [internet]. Hanover (MA): The Brain Aneurysm Foundation [accessed 2010 Dec 28]. [2 p]. Available:  
[http://www.bafound.org/Statistics\\_and\\_Facts](http://www.bafound.org/Statistics_and_Facts).
43. Fiorella D, Kelly M, Woo H. Flow diversion for intracranial aneurysm treatment. [internet]. Wayne (PA): Bryn Mawr Communications II LLC; 2009 Sep [accessed 2011 Feb 18]. [7 p]. Available:  
[http://bmctoday.net/evtoday/2009/09/article.asp?f=0909\\_07.php](http://bmctoday.net/evtoday/2009/09/article.asp?f=0909_07.php).

44. Pipeline embolization device - P100018. [internet]. Silver Spring (MD): U.S. Food and Drug Administration (FDA); 2011 Apr [accessed 2012 Jan 31]. [2 p]. Available: <http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/DeviceApprovalsandClearances/Recently-ApprovedDevices/ucm252130.htm>.
45. Flow diversion. [internet]. Dublin (Ireland): Covidien plc [accessed 2012 Nov 14]. [4 p]. Available: <http://www.ev3.net/neuro/us/flow-diversion/>.
46. Kan P, Siddiqui AH, Veznedaroglu E, et al. Early postmarket results after treatment of intracranial aneurysms with the pipeline embolization device: a U.S. multicenter experience. *Neurosurgery* 2012 Aug 31. PMID: 22948199
47. Colby GP, Lin LM, Gomez JF, et al. Immediate procedural outcomes in 35 consecutive pipeline embolization cases: a single-center, single-user experience. *J Neurointerv Surg* 2012 Mar 29. PMID: 22459178
48. Covidien's PUFs clinical trial data is favorable for device. *Med Device Daily* 2011 Aug 1.
49. Pipeline simplifies complex brain aneurysm treatment. *Med Dev Daily* 2011 Jun 13.
50. Colby GP, Lin LM, Paul AR, et al. Cost comparison of endovascular treatment of anterior circulation aneurysms with the pipeline embolization device versus stent-assisted coiling. *Neurosurgery* 2012 Nov;71(5):955-50. Epub 2012 Jul 16. PMID: 22806083
51. Yu SC, Kwok CK, Cheng PW, et al. Intracranial aneurysms: midterm outcome of pipeline embolization device--a prospective study in 143 patients with 178 aneurysms. *Radiology* 2012 Sep 20;Epub ahead of print. PMID: 22996749
52. Crobeddu E, Lanzino G, Kallmes DF, et al. Marked decrease in coil and stent utilization following introduction of flow diversion technology. *J Neurointerv Surg* 2012 Apr 27;Epub ahead of print. PMID: 22544822
53. NeuroTexas Institute first in central Texas to use Pipeline embolization device for treatment of large or giant wide-necked aneurysms. [internet]. Austin (TX): NeuroTexas Institute; 2012 Aug 23 [accessed 2012 Nov 20]. [3 p]. Available: <http://www.neurotexasinstitute.com/news/NeuroTexas-Institute-First-in-Central-Texas-to-Use-Pipeline%E2%AE-Embolization-Device-for-Treatment-of-Large-or-Giant-Wide-Necked-Aneurysms.aspx>.
54. Pipeline embolization device at Jefferson. [internet]. Philadelphia (PA): Thomas Jefferson University Hospitals [accessed 2012 Nov 20]. [1 p]. Available: <http://www.jeffersonhospital.org/Tests-and-Treatments/pipeline-embolization-device.aspx>.
55. Pipeline embolization device. [internet]. Atlanta (GA): Emory Healthcare [accessed 2012 Nov 20]. [2 p]. Available: <http://www.emoryhealthcare.org/medicaladvances/neurosciences-etma/pipeline.html>.
56. Tse MM, Yan B, Dowling RJ, et al. Current status of pipeline embolization device in the treatment of intracranial aneurysms: a review. *World Neurosurg* 2012 Oct 3;Epub ahead of print. PMID: 23041067
57. Understanding: treatment options. [internet]. Hanover (MA): The Brain Aneurysm Foundation [accessed 2012 Nov 14]. [2 p]. Available: <http://www.bafound.org/treatment-options>.
58. Understanding: treatment options - occlusion and bypass. [internet]. Hanover (MA): The Brain Aneurysm Foundation [accessed 2012 Nov 14]. [1 p]. Available: <http://www.bafound.org/treatment-options-1>.
59. Understanding: treatment options - endovascular embolization or coiling. [internet]. Hanover (MA): The Brain Aneurysm Foundation [accessed 2012 Nov 14]. [2 p]. Available: <http://www.bafound.org/treatment-options-2>.
60. Understanding: treatment options - other procedures. [internet]. Hanover (MA): The Brain Aneurysm Foundation [accessed 2012 Nov 14]. [2 p]. Available: <http://www.bafound.org/treatment-options-3>.
61. Expert Commenter 524. (ECRI Institute, Technology Assessment). Horizon Scanning Structured Comment Form. HS578 - Endovascular pipeline embolization device (PED) for treatment of brain aneurysms. 2012 Apr 10 [review date].
62. Expert Commenter 676. (PRI, Health Systems/Administration). Horizon Scanning Structured Comment Form. HS578 - Endovascular pipeline embolization device (PED) for treatment of brain aneurysms. 2012 Apr 18 [review date].
63. Expert Commenter 234. (External, Clinical). Horizon Scanning Structured Comment Form. HS578 - Endovascular pipeline embolization device (PED) for treatment of brain aneurysms. 2012 Mar 30 [review date].



64. Expert Commenter 424. (ECRI Institute, Technology Assessment). Horizon Scanning Structured Comment Form. HS578 - Endovascular pipeline embolization device (PED) for treatment of brain aneurysms. 2012 Apr 10 [review date].
65. Expert Commenter 400. (ECRI Institute, Applied Solutions Group). Horizon Scanning Structured Comment Form. HS578 - Endovascular pipeline embolization device (PED) for treatment of brain aneurysms. 2012 Apr 23 [review date].
66. Expert Commenter 1174. (ECRI Institute, Health Devices). Horizon Scanning Structured Comment Form. HS578 - Endovascular pipeline embolization device (PED) for treatment of brain aneurysms. 2012 Apr 10 [review date].
67. Expert Commenter 150. (External, Clinical). Horizon Scanning Structured Comment Form. HS578 - Endovascular pipeline embolization device (PED) for treatment of brain aneurysms. 2012 Apr 25 [review date].
68. Bartunek J, Vanderheyden M, Hill J, et al. Cells as biologics for cardiac repair in ischaemic heart failure. *Heart* 2010 May;96(10):792-800.
69. Chavakis E, Koyanagi M, Dimmeler S. Enhancing the outcome of cell therapy for cardiac repair: progress from bench to bedside and back. *Circulation* 2010 Jan;121(2):325-35.
70. Cardio3 Biosciences products pipeline. [internet]. Mont-Saint-Guibert (Belgium): Cardio3 Biosciences [accessed 2012 Nov 9]. [6 p]. Available: <http://www.c3bs.com/en/products-pipeline/productsipeline.html>.
71. Sheridan C. Mayo Clinic, Cardio3 report on heart failure therapy. *BioWorld International* 2010 Aug 18.
72. Bartunek J, Vanderheyden M, Henry S, et al. Second generation cell therapy for ischemic cardiomyopathy: the C-Cure programme. *EuroIntervention* 2009 May 21;5(Suppl E):E73.
73. Cardiovascular Drug News. MSCs reprogrammed to become cardiac precursor cells. [internet]. Princeton (NJ): Espicom USA Inc.; 2010 Aug 17 [accessed 2011 Feb 3]. [2 p]. Available: <http://www.espicom.com/cvdsn>.
74. Innovative heart-specified stem cell therapy improves heart function and fitness in heart failure patients. [internet]. Mont-Saint-Guibert (Belgium): Cardio3 BioSciences; 2011 Apr 5 [accessed 2011 Nov 14]. [3 p]. Available: [http://www.c3bs.com/images/pdf/acc\\_data-presentation\\_general\\_110405\\_final.pdf](http://www.c3bs.com/images/pdf/acc_data-presentation_general_110405_final.pdf).
75. Cardio3 BioSciences establishes US subsidiary in Rochester, MN. [internet]. Rochester (MN): Cardio3 BioSciences; 2011 Sep 22 [accessed 2011 Nov 14]. [3 p]. Available: [http://www.c3bs.com/images/stories/110922\\_Cardio3\\_Inc.pdf](http://www.c3bs.com/images/stories/110922_Cardio3_Inc.pdf).
76. Cardio3 reports positive six-month results with C-Cure in HF. *Cardiovasc Drug News* 2010 Nov 17.
77. Scottish Intercollegiate Guidelines Network (SIGN). Management of chronic heart failure. A national clinical guideline. Edinburgh (Scotland): Scottish Intercollegiate Guidelines Network (SIGN); 2007 Feb. 53 p. (SIGN publication; no. 95).
78. Mayo Clinic staff. Heart failure: treatments and drugs. [internet]. Rochester (MN): Mayo Foundation for Medical Education and Research (MFMER); 2009 Dec 23 [accessed 2011 Feb 9]. [4 p]. Available: <http://www.mayoclinic.com/health/heart-failure/DS00061/DSECTION=treatments-and-drugs>.
79. Expert Commenter 396. (ECRI Institute, Applied Solutions Group). Horizon Scanning Structured Comment Form. HS491 - Stem cell therapy (C-Cure) for treatment of heart failure. 2012 Apr 10 [review date].
80. Expert Commenter 654. (External, Health Systems/Administration). Horizon Scanning Structured Comment Form. HS491 - Stem cell therapy (C-Cure) for treatment of heart failure. 2012 Apr 24 [review date].
81. Expert Commenter 41. (External, Clinical). Horizon Scanning Structured Comment Form. HS491 - Stem cell therapy (C-Cure) for treatment of heart failure. 2012 Apr 18 [review date].
82. Expert Commenter 524. (ECRI Institute, Technology Assessment). Horizon Scanning Structured Comment Form. HS491 - Stem cell therapy (C-Cure) for treatment of heart failure. 2012 Apr 10 [review date].
83. Expert Commenter 413. (ECRI Institute, Health Devices). Horizon Scanning Structured Comment Form. HS491 - Stem cell therapy (C-Cure) for treatment of heart failure. 2012 Apr 10 [review date].
84. Expert Commenter 362. (External, Research). Horizon Scanning Structured Comment Form. HS491 - Stem cell therapy (C-Cure) for treatment of heart failure. 2012 Mar 27 [review date].



85. Total artificial heart facts. [internet]. Tucson (AZ): SynCardia Systems, Inc. [accessed 2012 Nov 9]. [2 p]. Available: <http://www.syncardia.com/Total-Facts/total-facts.html>.
86. Reliability second to none. [internet]. Tucson (AZ): SynCardia Systems, Inc. [accessed 2012 Nov 9]. [1 p]. Available: <http://www.syncardia.com/Medical-Professionals/reliability-second-to-none.html>.
87. 510(k) summary of safety and effectiveness data. CardioWest temporary total artificial heart. Rockville (MD): U.S. Food and Drug Administration (FDA); 2004 Oct 15. 28 p. Also available: <http://www.fda.gov>.
88. Zuckerman BD. (Director, Division of Cardiovascular Devices, Office of Device Evaluation, Center for Devices and Radiological Health, U.S. Food and Drug Administration). Premarket notification for Syncardia Systems, Inc. Syncardia temporary CardioWest Total Artificial Heart (TAH-t). P030011. 2004 Oct 15.
89. Clinical trials: the Freedom driver system. [internet]. Tucson (AZ): SynCardia Systems, Inc. [accessed 2012 Nov 9]. [3 p]. Available: <http://www.syncardia.com/Medical-Professionals/clinicaltrials.html>.
90. Freedom driver system receives CE mark to power SynCardia's total artificial heart in Europe. [internet]. Tucson (AZ): SynCardia Systems, Inc.; 2010 Mar 4 [accessed 2010 Mar 4]. [1 p]. Available: <http://www.syncardia.com/2010-Press-Release/freedom-driver-system-receives-ce-mark-to-power-syncardias-total-artificial-heart-in-europe.html>.
91. Friedline K, Hassinger P. Total artificial heart freedom driver in a patient with end-stage biventricular heart failure. AANA J 2012 Apr;80(2):105-12. Also available: <https://www.aanadc.com/newsandjournal/Documents/totalheart-0412-p105-112.pdf>.
92. Man without human heart hikes more than 400 miles. [internet]. Tucson (AZ): SynCardia Systems, Inc.; 2012 Aug 1 [accessed 2012 Nov 9]. [3 p]. Available: <http://www.syncardia.com/2012-Press-Releases/man-without-human-heart-hikes-more-than-400-miles.html>.
93. Jessup M, Abraham WT, Casey DE, et al. 2009 focused update: ACCF/AHA guidelines for the diagnosis and management of heart failure in adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation 2009 Apr 14;119(14):1977-2016. PMID: 19324967
94. Expert Commenter 396. (ECRI Institute, Applied Solutions Group). Horizon Scanning Structured Comment Form. HS334 - CardioWest total artificial heart with portable Freedom driver system as bridge to heart transplantation. 2012 Apr 13 [review date].
95. Expert Commenter 167. (External, Clinical). Horizon Scanning Structured Comment Form. HS334 - CardioWest total artificial heart with portable Freedom driver system as bridge to heart transplantation. 2012 Apr 18 [review date].
96. Expert Commenter 41. (External, Clinical). Horizon Scanning Structured Comment Form. HS334 - CardioWest total artificial heart with portable Freedom driver system as bridge to heart transplantation. 2012 Apr 19 [review date].
97. Expert Commenter 1011. (External, Health Systems/Administration). Horizon Scanning Structured Comment Form. HS334 - CardioWest total artificial heart with portable Freedom driver system as bridge to heart transplantation. 2012 Apr 18 [review date].
98. Expert Commenter 421. (ECRI Institute, Technology Assessment). Horizon Scanning Structured Comment Form. HS334 - CardioWest total artificial heart with portable Freedom driver system as bridge to heart transplantation. 2012 Apr 10 [review date].
99. Expert Commenter 403. (ECRI Institute, Health Devices). Horizon Scanning Structured Comment Form. HS334 - CardioWest total artificial heart with portable Freedom driver system as bridge to heart transplantation. 2012 Apr 10 [review date].
100. Expert Commenter 424. (ECRI Institute, Technology Assessment). Horizon Scanning Structured Comment Form. HS334 - CardioWest total artificial heart with portable Freedom driver system as bridge to heart transplantation. 2012 Apr 10 [review date].

101. Bisognano JD, Bakris G, Nadim MK, et al. Baroreflex activation therapy lowers blood pressure in patients with resistant hypertension: results from the double-blind, randomized, placebo-controlled Rheos pivotal trial. *J Am Coll Cardiol* 2011 Aug 9;58(7):765-73. PMID: 21816315
102. Esler MD, Krum H, Sobotka PA, et al. Renal sympathetic denervation in patients with treatment-resistant hypertension (the Symplicity HTN-2 trial): a randomised controlled trial. *Lancet* 2010 Dec 4-10;376(9756):1903-9.
103. Gewirtz JR, Bisognano JD. Catheter-based renal sympathetic denervation: a targeted approach to resistant hypertension. *Cardiol J* 2011;18(1):97-102. PMID: 21305496
104. About the procedure. [internet]. Minneapolis (MN): Medtronic, Inc. [accessed 2012 Nov 14]. [2 p]. Available: <http://www.medtronicrdn.com/intl/healthcare-professionals/about-rdn/about-the-procedure/index.htm>.
105. Medtronic starts landmark study of hypertension treatment. U.S. clinical trial of Symplicity Renal Denervation System enrolls first patient. [internet]. Minneapolis (MN): Medtronic, Inc.; 2011 Oct 26 [accessed 2012 Mar 6]. [3 p]. Available: <http://www.ardian.com/pdfs/HTN3%20first%20patient%20enrollment.pdf>.
106. The Symplicity catheter system. [internet]. Mountain View (CA): Medtronic, Inc. [accessed 2011 Jul 22]. [1 p]. Available: <http://www.ardian.com/ous/medical-professionals/system.shtml>.
107. The Symplicity renal denervation system. [internet]. Minneapolis (MN): Medtronic, Inc. [accessed 2012 Nov 14]. [2 p]. Available: <http://www.medtronicrdn.com/intl/healthcare-professionals/symplicity-rdn-system/index.htm>.
108. Symplicity overview. [internet]. Minneapolis (MN): Medtronic, Inc. [accessed 2012 Mar 7]. [1 p]. Available: <http://www.ardian.com/ous/patients/symplicity.shtml>.
109. Cohen DL, Townsend RR. Renal denervation revisited: promising treatment for resistant hypertension? *J Clin Hypertens (Greenwich)* 2011 Dec;13(12):931-2.
110. Symplicity HTN-1 Investigators. Catheter-based renal sympathetic denervation for resistant hypertension: durability of blood pressure reduction out to 24 months. *Hypertension* 2011 May;57(5):911-7. PMID: 21403086
111. Safe, superior, and sustained results with the Symplicity RDN system from the Symplicity HTN-1 & HTN-2 clinical trials. [internet]. Minneapolis (MN): Medtronic, Inc. [accessed 2012 Nov 14]. [3 p]. Available: <http://www.medtronicrdn.com/intl/healthcare-professionals/symplicity-rdn-system/symplicity-clinical-trial-data/index.htm>.
112. Medtronic completes acquisition of Ardian. [internet]. Mountain View (CA): Medtronic, Inc.; 2011 Jan 13 [accessed 2011 Jul 22]. [3 p]. Available: [http://www.ardian.com/pdfs/Ardian%20closing%20news%20release\\_FINAL\\_01\\_13\\_2011.pdf](http://www.ardian.com/pdfs/Ardian%20closing%20news%20release_FINAL_01_13_2011.pdf).
113. Medtronic Vascular. Renal denervation in patients with uncontrolled hypertension (SYMPPLICITY HTN-3). In: Clinicaltrials.gov [database online]. Bethesda (MD): National Library of Medicine (U.S.); 2000- [accessed 2012 Nov 9]. [3 p]. Available: <http://clinicaltrials.gov/ct2/show/NCT01418261> NLM Identifier: NCT01418261.
114. Medtronic gets go-ahead from FDA for study of novel treatment for high blood pressure. [internet]. Minneapolis (MN): Medtronic, Inc.; 2011 Jul 11 [accessed 2011 Jul 27]. [2 p]. Available: [http://www.medtronic.com/Newsroom/NewsReleaseDetails.do?itemId=1310400727504&lang=en\\_US](http://www.medtronic.com/Newsroom/NewsReleaseDetails.do?itemId=1310400727504&lang=en_US).
115. Geisler BP, Egan BM, Cohen JT, et al. Cost-effectiveness and clinical effectiveness of catheter-based renal denervation for resistant hypertension. *J Am Coll Cardiol* 2012 Oct 2;60(14):1271-7. Epub 2012 Sep 12. PMID: 22981547
116. National Heart, Lung, and Blood Institute (NHLBI). Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report [NIH Publication No. 04-5230]. Washington (DC): National Heart, Lung, and Blood Institute (NHLBI), National Institutes of Health (NIH); 2004 Aug. 87 p. Also available: <http://www.nhlbi.nih.gov/guidelines/hypertension/jnc7full.pdf>.

117. Expert Commenter 596. (External, Clinical). Horizon Scanning Structured Comment Form. HS613 - Radiofrequency ablation (Symplicity System) for renal denervation for treatment-resistant hypertension. 2012 Apr 24 [review date].
118. Expert Commenter 418. (ECRI Institute, Technology Assessment). Horizon Scanning Structured Comment Form. HS613 - Radiofrequency ablation (Symplicity System) for renal denervation for treatment-resistant hypertension. 2012 Apr 16 [review date].
119. Expert Commenter 676. (PRI, Health Systems/Administration). Horizon Scanning Structured Comment Form. HS613 - Radiofrequency ablation (Symplicity System) for renal denervation for treatment-resistant hypertension. 2012 Apr 18 [review date].
120. Expert Commenter 394. (ECRI Institute, Applied Solutions Group). Horizon Scanning Structured Comment Form. HS613 - Radiofrequency ablation (Symplicity System) for renal denervation for treatment-resistant hypertension. 2012 Apr 19 [review date].
121. Expert Commenter 409. (ECRI Institute, Health Devices). Horizon Scanning Structured Comment Form. HS613 - Radiofrequency ablation (Symplicity System) for renal denervation for treatment-resistant hypertension. 2012 Apr 20 [review date].
122. Expert Commenter 480. (External, Clinical). Horizon Scanning Structured Comment Form. HS613 - Radiofrequency ablation (Symplicity System) for renal denervation for treatment-resistant hypertension. 2012 Apr 23 [review date].
123. Expert Commenter 423. (ECRI Institute, Technology Assessment). Horizon Scanning Structured Comment Form. HS613 - Radiofrequency ablation (Symplicity System) for renal denervation for treatment-resistant hypertension. 2012 Apr 19 [review date].
124. Schmitto JD, Lee LS, Mokashi SA, et al. Functional mitral regurgitation. *Cardiol Rev* 2010 Nov-Dec;18(6):285-91. PMID: 20926937
125. Patient resources: conventional treatment options. [internet]. Kirkland (WA): Cardiac Dimensions, Inc. [accessed 2012 Jan 27]. [1 p]. Available: [http://www.cardiacdimensions.com/PatientResources/treatment\\_options.html](http://www.cardiacdimensions.com/PatientResources/treatment_options.html).
126. Feldman T, Cilingiroglu M. Percutaneous leaflet repair and annuloplasty for mitral regurgitation. *J Am Coll Cardiol* 2011 Feb 1;57(5):529-37. PMID: 21272742
127. Cardiac Dimensions, Inc. Physician resources: technology. [internet]. Kirkland (WA): Cardiac Dimensions, Inc. [accessed 2012 Nov 12]. [3 p]. Available: <http://www.cardiacdimensions.com/PhysicianResources/technology.html>.
128. Cardiac Dimensions, Inc. Physician resources: current studies. [internet]. Kirkland (WA): Cardiac Dimensions, Inc. [accessed 2012 Nov 12]. [1 p]. Available: [http://www.cardiacdimensions.com/PhysicianResources/current\\_studies.html](http://www.cardiacdimensions.com/PhysicianResources/current_studies.html).
129. Schofer J, Siminiak T, Haude M, et al. Percutaneous mitral annuloplasty for functional mitral regurgitation: results of the CARILLON Mitral Annuloplasty Device European Union Study. *Circulation* 2009 Jul 28;120(4):326-33. PMID: 19597051
130. Siminiak T, Wu JC, Haude M, et al. Treatment of functional mitral regurgitation by percutaneous annuloplasty: results of the TITAN Trial. *Eur J Heart Fail* 2012 Aug;14(8):931-8. PMID: 22613584
131. Cardiac Dimensions home page. [internet]. Kirkland (WA): Cardiac Dimensions, Inc. [accessed 2012 Jan 27]. [1 p]. Available: <http://www.cardiacdimensions.com/index.html>.
132. Cardiac Dimensions, Inc. Cardiac Dimensions receives CE mark approval for enhanced Carillon Mitral Contour System. [internet]. Kirkland (WA): Cardiac Dimensions, Inc.; 2011 Sep 29 [accessed 2012 Nov 14]. [2 p]. Available: [http://www.cardiacdimensions.com/Company/PressReleases/cardiac\\_dimensions\\_9\\_29\\_2011.html](http://www.cardiacdimensions.com/Company/PressReleases/cardiac_dimensions_9_29_2011.html).
133. Cardiac Dimensions, Inc. Cardiac Dimensions initiates European commercialization of Carillon Mitral Contour System. [internet]. Kirkland (WA): Cardiac Dimensions, Inc.; 2012 Sep 28 [accessed 2012 Nov 14]. [2 p]. Available: [http://www.cardiacdimensions.com/Company/PressReleases/cardiac\\_dimensions\\_09\\_28\\_2012.html](http://www.cardiacdimensions.com/Company/PressReleases/cardiac_dimensions_09_28_2012.html).

134. American College of Cardiology, American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 1998 Guidelines for the Management of Patients with Valvular Heart Disease), Society of Cardiovascular Anesthesiologists, et al. ACC/AHA 2006 guidelines for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 1998 Guidelines for the Management of Patients with Valvular Heart Disease) developed in collaboration with the Society of Cardiovascular Anesthesiologists endorsed by the Society for Cardiovascular Angiography and Interventions and the Society of Thoracic Surgeons. *J Am Coll Cardiol* 2006 Aug 1;48(3):e1-148. PMID: 16875962
135. Expert Commenter 654. (External, Health Systems/Administration). Horizon Scanning Structured Comment Form. HS160 - Percutaneous annuloplasty (Carillon Mitral Contour System) to treat functional mitral regurgitation. 2012 Mar 23 [review date].
136. Expert Commenter 524. (ECRI Institute, Technology Assessment). Horizon Scanning Structured Comment Form. HS160 - Percutaneous annuloplasty (Carillon Mitral Contour System) to treat functional mitral regurgitation. 2012 Mar 23 [review date].
137. Expert Commenter 642. (PRI, Clinical). Horizon Scanning Structured Comment Form. HS160 - Percutaneous annuloplasty (Carillon Mitral Contour System) to treat functional mitral regurgitation. 2012 Mar 23 [review date].
138. Expert Commenter 403. (ECRI Institute, Health Devices). Horizon Scanning Structured Comment Form. HS160 - Percutaneous annuloplasty (Carillon Mitral Contour System) to treat functional mitral regurgitation. 2012 Apr 10 [review date].
139. Expert Commenter 400. (ECRI Institute, Applied Solutions Group). Horizon Scanning Structured Comment Form. HS160 - Percutaneous annuloplasty (Carillon Mitral Contour System) to treat functional mitral regurgitation. 2012 Apr 10 [review date].
140. Expert Commenter 476. (External, Clinical). Horizon Scanning Structured Comment Form. HS160 - Percutaneous annuloplasty (Carillon Mitral Contour System) to treat functional mitral regurgitation. 2012 Apr 26 [review date].
141. Ren X. Aortic stenosis treatment & management. In: Medscape Reference [internet]. New York (NY): WebMD, LLC [accessed 2012 Nov 12]. [10 p]. Available: <http://emedicine.medscape.com/article/150638-treatment>.
142. Medtronic, Inc. Severe aortic stenosis treatment options. [internet]. Minneapolis (MN): Medtronic, Inc. [accessed 2012 Nov 14]. [2 p]. Available: <http://www.medtronic.com/corevalve/ous/treatment-options.html>.
143. Treatment options for heart valve disease: open chest heart valve surgery. In: YourHeartValve.com [internet]. Irvine (CA): Edwards Lifesciences LLC [accessed 2012 Nov 12]. [2 p]. Available: <http://www.yourheartvalve.com/treatmentoptions/Pages/openchestsurgery.aspx>.
144. Treatment options for heart valve disease: the transcatheter approach (TAVR). In: YourHeartValve.com [internet]. Irvine (CA): Edwards Lifesciences LLC [accessed 2012 Nov 12]. [11 p]. Available: <http://www.yourheartvalve.com/treatmentoptions/Pages/transcatheterapproach.aspx>.
145. CoreValve system. [internet]. Minneapolis (MN): Medtronic, Inc. [accessed 2011 Sep 22]. [2 p]. Available: <http://www.medtronic.com/corevalve/ous/system.html>.
146. ECRI Institute. Transcatheter aortic valve replacement. Plymouth Meeting (PA): ECRI Institute; 2010 Sep 23. 8 p. (Health Technology Forecast).
147. CoreValve transcatheter aortic valve implantation. Minneapolis (MN): Medtronic, Inc.; 2011. 15 p. Also available: [http://www.medtronic.com/corevalve/ous/downloads/201000846a\\_EE.pdf](http://www.medtronic.com/corevalve/ous/downloads/201000846a_EE.pdf).
148. Medtronic, Inc. Medtronic gains CE mark for CoreValve Evolut 23mm. [internet]. Minneapolis (MN): Medtronic, Inc.; 2012 Sep 26 [accessed 2012 Nov 14]. [1 p]. Available: [http://www.medtronic.com/Newsroom/NewsReleaseDetails.do?itemId=1348597971971&lang=en\\_US](http://www.medtronic.com/Newsroom/NewsReleaseDetails.do?itemId=1348597971971&lang=en_US).
149. ECRI Institute. Transcatheter aortic valve implantation, an option where there is none. *Health Technol Trends* 2011 Jun;23(6):1-3, 6.

150. Medtronic Vascular. Safety and efficacy study of the Medtronic CoreValve system in the treatment of symptomatic severe aortic stenosis in high risk and very high risk subjects who need aortic valve replacement. In: ClinicalTrials.gov [database online]. Bethesda (MD): National Library of Medicine (U.S.); 2000- [accessed 2011 Sep 22]. [6 p]. Available: <http://clinicaltrials.gov/ct2/show/NCT01240902> NLM Identifier: NCT01240902.
151. Medtronic Cardiovascular. Safety and efficacy continued access study of the Medtronic CoreValve System in the treatment of symptomatic severe aortic stenosis in very high risk subjects and high risk subjects who need aortic valve replacement. In: ClinicalTrials.gov [database online]. Bethesda (MD): National Library of Medicine (U.S.); 2000- [accessed 2012 Nov 14]. [4 p]. Available: <http://www.clinicaltrials.gov/ct2/show/NCT01531374> NLM Identifier: NCT01531374.
152. Medtronic Cardiovascular. Safety and efficacy study of the Medtronic CoreValve System in the treatment of severe, symptomatic aortic stenosis in intermediate risk subjects who need aortic valve replacement (SURTAVI). In: ClinicalTrials.gov [database online]. Bethesda (MD): National Library of Medicine (U.S.); 2000- [accessed 2012 Nov 14]. [5 p]. Available: <http://www.clinicaltrials.gov/ct2/show/NCT01586910> NLM Identifier: NCT01586910.
153. Medtronic, Inc. New study results show high survival rates and improved quality of life for patients with Medtronic CoreValve System. [internet]. Minneapolis (MN): Medtronic, Inc.; 2012 Oct 22 [accessed 2012 Nov 14]. [2 p]. Available: [http://www.medtronic.com/Newsroom/NewsReleaseDetails.do?itemId=1350591608535&lang=en\\_US](http://www.medtronic.com/Newsroom/NewsReleaseDetails.do?itemId=1350591608535&lang=en_US).
154. Medtronic Bakken Research Center. CoreValve advance international post market study. In: ClinicalTrials.gov [database online]. Bethesda (MD): National Library of Medicine (U.S.); 2000- [accessed 2012 Nov 12]. [3 p]. Available: <http://clinicaltrials.gov/ct2/show/NCT01074658> NLM Identifier: NCT01074658.
155. Edwards Lifesciences LLC. Edwards SAPIEN transcatheter heart valve. [internet]. Irvine (CA): Edwards Lifesciences LLC [accessed 2012 Nov 12]. [3 p]. Available: <http://www.edwards.com/Products/TranscatheterValve/Pages/sapienthv.aspx>.
156. Edwards Lifesciences Corporation. Edwards SAPIEN transcatheter heart valve: transfemoral product overview. [internet]. Irvine (CA): Edwards Lifesciences Corporation [accessed 2012 Nov 12]. [6 p]. Available: <http://www.edwards.com/Products/TranscatheterValve/Pages/transfemoral.aspx>.
157. Edwards Lifesciences Corporation. Edwards SAPIEN transcatheter heart valve: transapical product overview. [internet]. Irvine (CA): Edwards Lifesciences Corporation [accessed 2012 Nov 12]. [5 p]. Available: <http://www.edwards.com/products/transcathetervalve/Pages/transapical.aspx>.
158. Transcatheter aortic valve replacement [patient brochure]. Irvine (CA): Edwards Lifesciences LLC; 20 p.
159. Edwards Lifesciences achieves primary endpoint in transcatheter valve study of high-risk surgical patients. [internet]. Irvine (CA): Edwards Lifesciences LLC; 2011 Apr 3 [accessed 2011 Oct 31]. [2 p]. Available: <http://www.edwards.com/newsroom/Pages/NR20110403.aspx>.
160. Edwards Lifesciences receives FDA approval for first catheter-based aortic heart valve in the U.S. [internet]. Irvine (CA): Edwards Lifesciences LLC; 2011 Nov 2 [accessed 2011 Nov 3]. [2 p]. Available: <http://www.edwards.com/newsroom/Pages/NR20111102.aspx>.
161. FDA approves expanded indication for Edwards Lifesciences' transcatheter valve. [internet]. Irvine (CA): Edwards Lifesciences Corporation; 2012 Oct 19 [accessed 2012 Oct 24]. [2 p]. Available: <http://www.edwards.com/newsroom/Pages/NR20121019.aspx>.
162. U.S. Food and Drug Administration (FDA). Edwards SAPIEN Transcatheter Heart Valve (THV) - P110021. [internet]. Silver Spring (MD): U.S. Food and Drug Administration (FDA); [accessed 2012 Nov 14]. [2 p]. Available: <http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/DeviceApprovalsandClearances/Recently-ApprovedDevices/ucm327342.htm>.
163. Reynolds MR. Cost effectiveness of transcatheter aortic valve replacement compared with surgical aortic valve replacement in patients with severe aortic stenosis: results from the PARTNER Trial (Cohort A) [slide set]. New York (NY): Cardiovascular Research Foundation; 2011 Nov 7. 32 p. Also available: <http://tctmd.com/show.aspx?id=108809>.



164. Centers for Medicare & Medicaid Services (CMS). Decision memo for transcatheter aortic valve replacement (TAVR) (CAG-00430N). Baltimore (MD): Centers for Medicare & Medicaid Services (CMS); 2012. 41 p. Also available: [http://www.cms.gov/medicare-coverage-database/shared/handlers/highwire.ashx?url=http://www.cms.gov/medicare-coverage-database/details/nca-decision-memo.aspx@@@NCAId\\$\\$\\$257&session=w12ft45id1pbf55dnui3j2m&kq=1718690667](http://www.cms.gov/medicare-coverage-database/shared/handlers/highwire.ashx?url=http://www.cms.gov/medicare-coverage-database/details/nca-decision-memo.aspx@@@NCAId$$$257&session=w12ft45id1pbf55dnui3j2m&kq=1718690667).
165. Treatment options for heart valve disease: medications. In: YourHeartValve.com [internet]. Irvine (CA): Edwards Lifesciences LLC [accessed 2012 Nov 12]. [1 p]. Available: <http://www.yourheartvalve.com/treatmentoptions/Pages/medication.aspx>.
166. Expert Commenter 396. (ECRI Institute, Applied Solutions Group). Horizon Scanning Structured Comment Form. HS914 - Transcatheter aortic valve (CoreValve) implantation for treatment of severe aortic stenosis. 2012 Apr 13 [review date].
167. Expert Commenter 41. (External, Clinical). Horizon Scanning Structured Comment Form. HS914 - Transcatheter aortic valve (CoreValve) implantation for treatment of severe aortic stenosis. 2012 Apr 23 [review date].
168. Expert Commenter 524. (ECRI Institute, Technology Assessment). Horizon Scanning Structured Comment Form. HS914 - Transcatheter aortic valve (CoreValve) implantation for treatment of severe aortic stenosis. 2012 Apr 13 [review date].
169. Expert Commenter 676. (PRI, Health Systems/Administration). Horizon Scanning Structured Comment Form. HS914 - Transcatheter aortic valve (CoreValve) implantation for treatment of severe aortic stenosis. 2012 Apr 5 [review date].
170. Expert Commenter 278. (External, Clinical). Horizon Scanning Structured Comment Form. HS914 - Transcatheter aortic valve (CoreValve) implantation for treatment of severe aortic stenosis. 2012 Apr 23 [review date].
171. Expert Commenter 1174. (ECRI Institute, Health Devices). Horizon Scanning Structured Comment Form. HS914 - Transcatheter aortic valve (CoreValve) implantation for treatment of severe aortic stenosis. 2012 Apr 10 [review date].
172. Expert Commenter 423. (ECRI Institute, Technology Assessment). Horizon Scanning Structured Comment Form. HS914 - Transcatheter aortic valve (CoreValve) implantation for treatment of severe aortic stenosis. 2012 Apr 13 [review date].
173. Expert Commenter 596. (External, Clinical). Horizon Scanning Structured Comment Form. HS22 - Transcatheter aortic valve replacement (SAPIEN) for treatment of severe aortic valve stenosis. 2012 Jan 17 [review date].
174. Expert Commenter 524. (ECRI Institute, Technology Assessment). Horizon Scanning Structured Comment Form. HS22 - Transcatheter aortic valve replacement (SAPIEN) for treatment of severe aortic valve stenosis. 2012 Jan 10 [review date].
175. Expert Commenter 411. (ECRI Institute, Health Devices). Horizon Scanning Structured Comment Form. HS22 - Transcatheter aortic valve replacement (SAPIEN) for treatment of severe aortic valve stenosis. 2012 Jan 17 [review date].
176. Expert Commenter 441. (PRI, Health Systems/Administration). Horizon Scanning Structured Comment Form. HS22 - Transcatheter aortic valve replacement (SAPIEN) for treatment of severe aortic valve stenosis. 2011 Dec 15 [review date].
177. Expert Commenter 395. (ECRI Institute, Applied Solutions Group). Horizon Scanning Structured Comment Form. HS22 - Transcatheter aortic valve replacement (SAPIEN) for treatment of severe aortic valve stenosis. 2012 Jan 10 [review date].
178. Expert Commenter 278. (External, Clinical). Horizon Scanning Structured Comment Form. HS22 - Transcatheter aortic valve replacement (SAPIEN) for treatment of severe aortic valve stenosis. 2012 Jan 23 [review date].
179. Whitlow PL, Feldman T, Pedersen WR, et al. Acute and 12-month results with catheter-based mitral valve leaflet repair: the EVEREST II (endovascular valve edge-to-edge repair) high risk study. J Am Coll Cardiol 2012 Jan 10;59(2):130-9. PMID: 22222076
180. Jilaihawi H, Hussaini A, Kar S. MitraClip: a novel percutaneous approach to mitral valve repair. J Zhejiang Univ Sci B 2011 Aug;12(8):633-7. PMID: MEDLINE - PMID:21796803

181. Vahanian A, Iung B. 'Edge to edge' percutaneous mitral valve repair in mitral regurgitation: it can be done but should it be done? *Eur Heart J* 2010 Jun;31(11):1301-4. PMID: 20385570
182. Data from landmark clinical trial of Abbott's MitraClip system demonstrate durable clinical benefits for patients with mitral regurgitation two years after treatment. [internet]. New Orleans (LA): Abbott; 2011 Apr 4 [accessed 2011 Nov 14]. [3 p]. Available: <http://www.abbott.com/PressRelease/2011Apr04.htm>.
183. Feldman T, Kar S, Rinaldi M, et al. Percutaneous mitral repair with the MitraClip system: safety and midterm durability in the initial EVEREST (Endovascular Valve Edge-to-Edge REpair Study) cohort. *J Am Coll Cardiol* 2009 Aug 18;54(8):686-94. PMID: 19679246
184. MitraClip mitral valve repair system. [internet]. Abbott Park (IL): Abbott Vascular; [accessed 2011 Nov 14]. [2 p]. Available: <http://www.abbottvascular.com/int/mitraclip.html>.
185. Abbott recall followed by FDA request for more Mitraclip data. *Devices Diagn Lett* 2011 Jul 25;38(29).
186. Evalve. Pivotal study of a percutaneous mitral valve repair system (EVEREST II). In: ClinicalTrials.gov [database online]. Bethesda (MD): National Library of Medicine (U.S.); 2000- [accessed 2012 Nov 12]. [6 p]. Available: <http://www.clinicaltrials.gov/ct2/show/NCT00209274> NLM Identifier: NCT00209274.
187. Feldman T, Foster E, Qureshi M, et al. The EVEREST II randomized controlled trial (RCT): three year outcomes. *J Am Coll Cardiol* 2012 Oct;60(17 Suppl B):TCT-788. Also available: <http://content.onlinejacc.org/article.aspx?articleID=1384057>.
188. Reynolds M, Galper B, Apruzzese P, et al. Cost effectiveness of the MitraClip compared with mitral valve surgery: 12-month results from the EVEREST II randomized controlled trial. *J Am Coll Cardiol* 2012 Oct;60(17 Suppl B):TCT-786. Also available: <http://content.onlinejacc.org/article.aspx?articleID=1384057>.
189. Expert Commenter 278. (External, Clinical). Horizon Scanning Structured Comment Form. HS330 - Transcatheter mitral valve repair (MitraClip) for treatment of mitral regurgitation. 2012 Sep 10 [review date].
190. Expert Commenter 395. (ECRI Institute, Applied Solutions Group). Horizon Scanning Structured Comment Form. HS330 - Transcatheter mitral valve repair (MitraClip) for treatment of mitral regurgitation. 2012 Sep 13 [review date].
191. Expert Commenter 403. (ECRI Institute, Health Devices). Horizon Scanning Structured Comment Form. HS330 - Transcatheter mitral valve repair (MitraClip) for treatment of mitral regurgitation. 2012 Sep 17 [review date].
192. Expert Commenter 418. (ECRI Institute, Technology Assessment). Horizon Scanning Structured Comment Form. HS330 - Transcatheter mitral valve repair (MitraClip) for treatment of mitral regurgitation. 2012 Sep 13 [review date].
193. Expert Commenter 423. (ECRI Institute, Technology Assessment). Horizon Scanning Structured Comment Form. HS330 - Transcatheter mitral valve repair (MitraClip) for treatment of mitral regurgitation. 2012 Sep 18 [review date].
194. Expert Commenter 433. (External, Health Systems/Administration). Horizon Scanning Structured Comment Form. HS330 - Transcatheter mitral valve repair (MitraClip) for treatment of mitral regurgitation. 2012 Oct 10 [review date].
195. Expert Commenter 1193. (ECRI Institute, Technology Assessment). Horizon Scanning Structured Comment Form. HS330 - Transcatheter mitral valve repair (MitraClip) for treatment of mitral regurgitation. 2012 Sep 17 [review date].
196. Expert Commenter 1195. (External, Research/Scientific/Technical). Horizon Scanning Structured Comment Form. HS330 - Transcatheter mitral valve repair (MitraClip) for treatment of mitral regurgitation. 2012 Sep 18 [review date].